



*For over a decade satisfied customers have made FlexX their premier choice in structure-based drug design software. Its ability to accurately predict the binding mode of a potential drug candidate with a receptor in less than 5 seconds makes it a must-have if you want to reliably perform ultra-high throughput docking and screening.*

## About FlexX

FlexX is one of the most established protein-ligand docking tools in the literature. Cited hundreds of times, it has proved to be highly successful in numerous drug discovery applications. [1-4; for further references, please visit <http://www.biosolveit.de/references>] Several sub-nanomolar inhibitors have been discovered with FlexX and are on the market after having proved their potential as a drug. [5,6]

The technology behind FlexX is based on a robust incremental construction algorithm. The ligand is decomposed into pieces and then flexibly built up in the active site, using a variety of placement strategies. The poses are scored based on a variety of different scoring functions, and all possible data, incl. details about interactions made available for analysis by the user.

## Performance

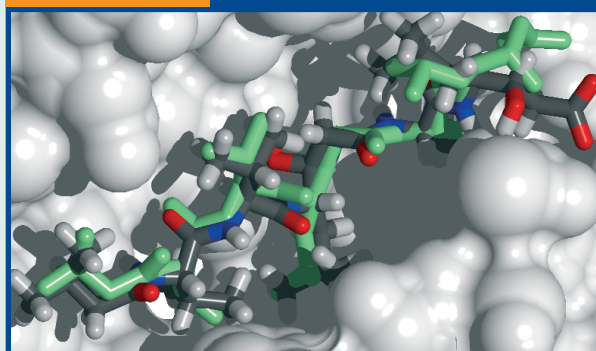
The most essential feature of a docking algorithm is to predict the correct pose of a ligand in the active site. It is standard procedure to test and calibrate the software on a representative data set. Recent studies identified many pitfalls for the assessment of docking software. [7]

Therefore, for an objective comparison of the three leading docking programs we show the performance of each docking algorithm on the data set with which it has been calibrated. In the region of docking accuracy of most interest to a medicinal chemist ( $\leq 2 \text{ \AA}$ ), all three tools perform comparably well with respect to accuracy.

## Screening

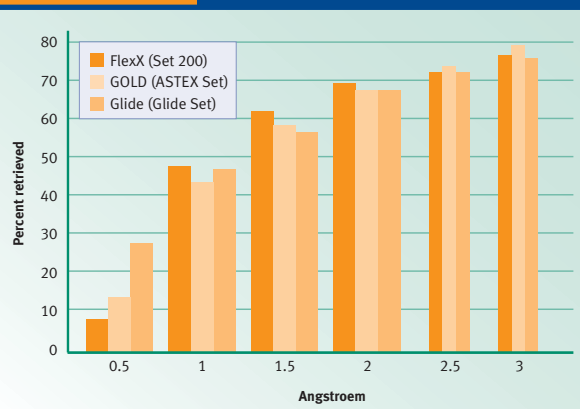
Another very important feature of a docking algorithm is to distinguish between active and inactive compounds in a virtual screen. In an independent study conducted by GSK in 2005, [8] FlexX was the best performing program, showing an average enrichment factor of above 3. This study was repeated using FlexX Release 2 and shows an enrichment which improved by 30% compared to version 1.10.1, used in the original publication.

### Pose Prediction



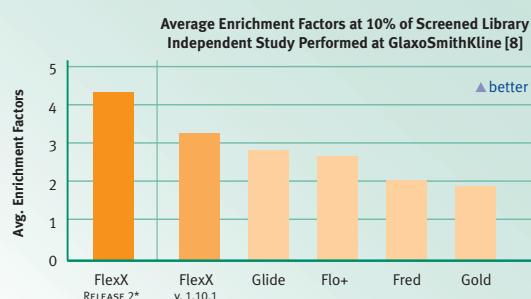
An excellent example of FlexX's ability to dock very flexible ligands: Pepstatin (PDB code 1PSO) docked into Pepsin 3a. The docked structure (in light green) has an RMSD of only 1.3 Å.

### Performance



Docking accuracy: FlexX reliably docks a ligand with less than 2 Å from the biological structure [11].

### Enrichment



Screening: FlexX has proved to be the tool of choice when it comes to finding actives in a database

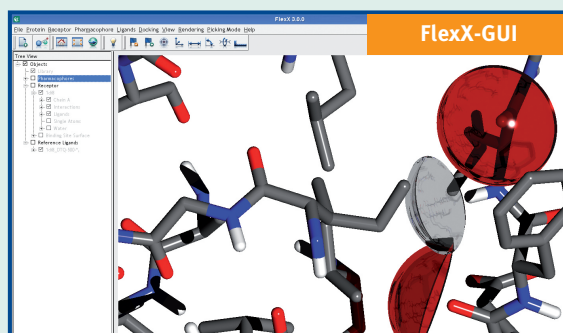
\* Please note that this enrichment factor has been calculated in house for one scoring function whereas the value for 1.10.1 is the best of all available scoring functions, cp. ref. [8].



## Speed

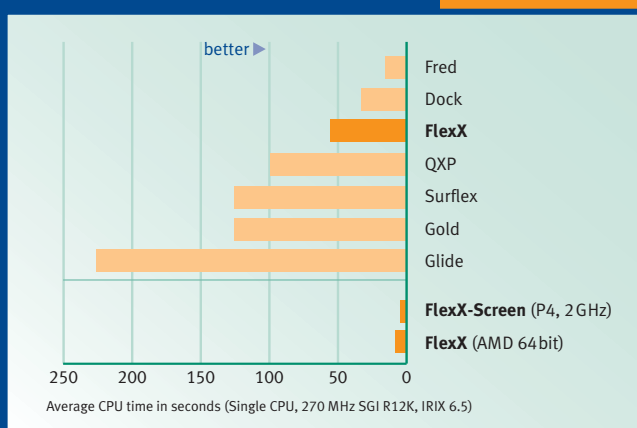
A third requirement of a successful docking algorithm, and this is what puts FlexX miles ahead of its competitors, is that it has to be fast. FlexX is tremendously fast: A study performed by Didier Rognan at the CNRS in France [9] showed that FlexX was already among the fastest docking tools on the market, being twice as fast as Gold and Surflex and about three times as fast as Glide.

A recent performance study with the 64bit version of FlexX using a state-of-the-art AMD Athlon CPU brought a further boost in speed, resulting in a docking time of 5 seconds per molecule. [10]



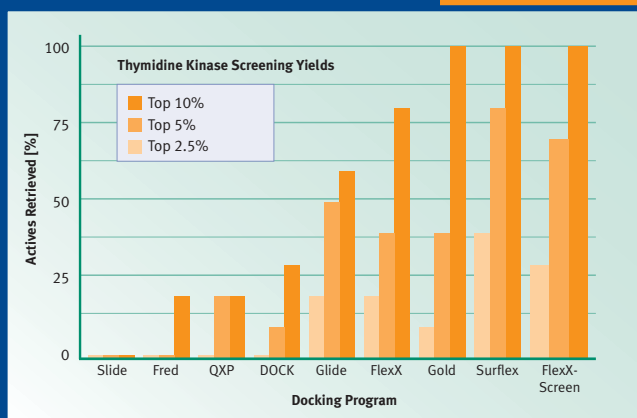
The new FlexX comes with an intuitive Graphical User Interface. Shown here is the pharmacophore definition of the hinge region of a CDK2 receptor (PDB code 1DI8) with a hydrogen bond donor (transparent) and acceptor interaction surfaces (red).

### Speed



Speed: An earlier independent benchmark test on outdated technology [9] has shown that FlexX was among the fastest docking engines. A more recent state-of-the-art study [10] puts FlexX way ahead of the competition and with its new booster module FlexX-Screen it sets new standards at about one second per compound or faster, including flexible addressing of torsion angles.

### FlexX-Screen



FlexX-Screen [12] has proved to be as good or better than competitors' products, such as Glide, Gold or Surflex, only much faster [9], data for FlexX-Screen computed on the original data set).

## Complementary to FlexX

There are several modules available that will enhance the integration of FlexX into your modeling toolbox:

**FlexX-Pharm:** Docking under receptor-based pharmacophore constraints. Easily define interaction constraints with a few mouse clicks; or define spatial constraints - optionally using SMARTS substructure expressions.

**FlexX-Ensemble:** Extend your docking to include receptor flexibility. This module (formerly FlexE) simultaneously docks into an ensemble of active site conformations and thus allows for an induced fit while placing the ligand.

**FlexX-Screen:** Docking at warp Speed. Due to several algorithmic tweaks, FlexX-Screen is up to 10 times faster than FlexX, with about the same accuracy. Indispensable for ultra-high throughput structure-based design.

**FlexXC:** Combinatorial libraries can be docked even more efficiently using this module.

**FlexX-Permute:** Automatically dock all tautomers, isomers etc.

**PyFlexX:** The Python version of FlexX provides even more powerful scripting capabilities.

## Graphical User Interfaces

The latest version of FlexX incorporates an intuitive **Graphical User Interface** that sets new standards in user friendliness and functionality.

Tripos continues to offer a graphical user interface to FlexX within its leading, integrated modeling environment **SYBYL**®.

**MOE**®, the renowned Molecular Operating Environment by Chemical Computing Group, Inc. supports FlexX through an intuitive interface, which allows FlexX calculations to be set up, run and analyzed from within MOE.

**DDB** (the Docking Database) is BioSolveIT's graphical data mining environment to post-process docking results. Its powerful features help leverage the medicinal chemist's intuition.

### References

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- [12] Schellhammer, I. et al., *Proteins*, **57**, 504-517 (2004)

### Acknowledgments

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### Technical Requirements

FlexX is available for Linux x86, SGI IRIX, Sun Solaris, HP-UX Itanium2 and Windows platforms. Minimum requirement is a 500 MHz CPU (Linux) with 128 MByte RAM and 30 MByte of disk space. For more details, please visit [www.biosolveit.de/flexx/sys-req.html](http://www.biosolveit.de/flexx/sys-req.html)

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