



www.ccdc.cam.ac.uk



GOLD

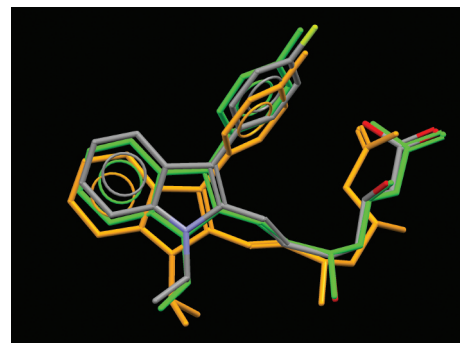
An accurate and versatile
solution for protein-ligand docking

Rigorously validated, and highly configurable, GOLD has proven success in virtual screening, lead optimisation, and identifying the correct binding mode of active molecules.

Accuracy

Comprehensively validated and widely used, GOLD enables you to make confident binding mode predictions, and achieve high database enrichments.

- **Accurate pose prediction:** GOLD [1,2] reliably identifies the correct binding mode for a large range of test set cases. For example, against the Astex Diverse set, a test set containing 85 diverse, high quality drug-like complexes, GOLD reproduces the observed binding mode within 2.0Å for 81% of the structures [3]. This and other extensively checked validation test sets can be freely downloaded from the CCDC website.
- **Objective comparisons:** GOLD has been shown to perform favourably against other docking tools in a number of independent studies [4,5]. Additionally, CCDC researchers, in collaboration with Astex, have been in the forefront in recommending ways in which comparisons can be conducted objectively [6,7].
- **Widely trusted:** With more than 600 published pharmaceutical research applications, GOLD's success has been extensively demonstrated. All publications, including studies against GPCR's [8,9], can be found within WebCite – a searchable repository of research publications available from the CCDC website.



Results of GoldScore (green) and ChemScore (orange) dockings of 1HWI, taken from the Astex Diverse Set. The native ligand is coloured by element. The subtleties of using different scoring functions can be seen: the top-ranked ChemScore pose is good, RMSd 1.16, however the top-ranked GoldScore pose is better, RMSd 0.37.

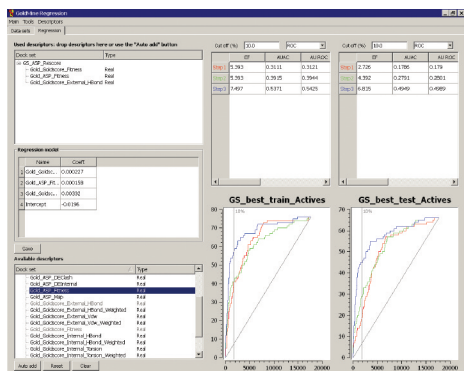


Results of a GoldScore docking showing the importance of considering ring conformations. GOLD performs well when the ring conformation is not considered (red solution) however the pose can be further optimised by using GOLD's ring conformation library (green solution). Native ligand pose coloured by element.

Versatility

GOLD is highly configurable allowing you to take full advantage of your knowledge of a protein-ligand system in order to maximise docking performance.

- **Diverse applicability:** Scoring functions are optimised differently and one may outperform another for a given receptor class, or binding motif. With a wide range of available scoring functions GOLD provides high performance across a diverse range of receptor types. In addition, GOLD offers extensive options for customising or implementing new scoring functions through a Scoring Function Application Programming Interface.
- **Customisable parameters and protocols:** GOLD enables complete user control over speed versus accuracy settings, from efficient virtual screening of large compound libraries, to highly accurate exhaustive sampling for lead optimisation. Select from pre-defined, or implement your own, target specific protocols, and benefit from special parameterisation for kinases and heme-containing [10] proteins.
- **Receptor Flexibility:** Even small protein conformation changes can have a dramatic effect on ligand binding. GOLD accounts for receptor flexibility through use of soft potentials, side-chain flexibility and most importantly ensemble docking. Using a novel methodology which avoids computationally expensive sequential docking of ligands into multiple protein structures, ensemble docking with GOLD solves the challenge of model selection.
- **Constraints:** A wide range of constraints can be employed to ensure, for example, that key H-bond interactions are fulfilled, or to bias docking results towards a known binding motif [11]. Unfavourable conformations can be eliminated by utilising customisable torsion angle distributions and an extensive library of ring conformations extracted from the Cambridge Structural Database.



GoldMine features regression tools for creating target-specific rescoring functions.

Ease of Use

GOLD can be easily integrated within your existing workflows to provide convenient docking setup and the efficient analysis of results.

- Simple docking setup:** The Hermes interface provides advanced visualisation options and interactive docking setup. A docking wizard is available which will guide you through the essential configuration steps from preparing protein and ligand input files to selecting the optimal docking protocols. For experienced users, a comprehensive interface allows fine grain control of docking parameters and speed versus accuracy settings.
- Seamless integration:** native interfaces allow docking runs to be set up and submitted directly from within 3rd party modelling environments, including Discovery Studio from Accelrys, and Chemical Computing Group's MOE. Integration allows GOLD users to benefit from the model preparation and post-docking tools provided within these platforms. Pipeline pilot components and a command line version of GOLD are also available.
- Embedded post-processing tools:** Scoring functions alone should not be relied upon for identification of actives. GoldMine allows you to calculate a vast range of descriptors, then filter your results in a sophisticated manner in order to identify docking poses that satisfy favourable properties. Enrichment metrics (e.g. AUC, ROC, BEDROC) can be generated interactively for virtual screens. Scoring function components and other descriptors may be combined using multiple regression to create discrimination models, target-specific scoring functions, and 3D QSAR models.

Case Studies

Case studies demonstrating GOLD's effectiveness in solving a range of problems are available from the CCDC website: http://www.ccdc.cam.ac.uk/case_studies



References

- [1] G. Jones, P. Willett, R. C. Glen, *J. Mol. Biol.*, 245, 43-53, 1995; G. Jones, P. Willett, R. C. Glen, A. R. Leach, R. Taylor, *J. Mol. Biol.*, 267, 727-748, 1997.
- [2] M. L. Verdonk, J. C. Cole, M. J. Hartshorn, C. W. Murray, R. D. Taylor, *Proteins*, 52, 609-623, 2003.
- [3] M. J. Hartshorn, M. L. Verdonk, G. Chessari, S. C. Brewerton, W. T. M. Mooij, P. N. Mortenson, C. W. Murray, *J. Med. Chem.*, 50, 726-741, 2007.
- [4] C. R. Corbeil, N. Moitessier, *J. Chem. Inf. Model.* 2009, 49, 997-1009.
- [5] T. Cheng, X. Li, Y. Li, R. Liu, R. Wang, *J. Chem. Inf. Model.* 2009, 49, 997-1009.
- [6] J. C. Cole, C. W. Murray, J. W. M. Nissink, R. D. Taylor, R. Taylor, *Proteins*, 60, 325-332, 2005.
- [7] J. W. Liebeschuetz, *J. Comput. -Aided Mol. Des.*, 22, 229-238, 2008.
- [8] G. Li, K. M. Haney, G. E. Kellogg, Y. Zhang, *J. Chem. Inf. Model.* 2009, 49, 120-132.
- [9] J. R. Shah, P. D. Mosier, B. L. Roth, G. E. Kellogg, R. B. Westkaemper, *Bioorg. Med. Chem.* 2009, 17, 6496-6504.
- [10] S. B. Kirton, C. W. Murray, M. L. Verdonk, R. D. Taylor, *Proteins*, 58, 836-844, 2005.
- [11] S. C. Brewerton, *Curr. Opin. Drug Discov. Devel.* 11(3):356-64, 2008.

Evaluations

To request an evaluation copy of GOLD, please contact admin@ccdc.cam.ac.uk

Supported platforms

GOLD Suite programs (Hermes, GOLD and GoldMine) are supported on the following platforms and operating systems:

Windows – Intel compatible, 32 bit, Windows 2000, XP, Vista, and 7

Linux – Intel compatible, 32 & 64 bit:

- RedHat Enterprise 4 and 5
- SuSe Linux Enterprise [Desktop|Server] 10
- Debian 4.0, and 5.0

Grid-enabled

GOLD can be run under PVM and used with standard queuing software packages, e.g., Sun Grid Engine, PBS Pro.

Related products

CCDC offer a range of integrated products to aid structure-based design. The following tools can be accessed directly through the Hermes graphical user interface:

Relibase+: Improve confidence in your model selection, and identify potential targets for cross activity by analysing a fully curated version of the PDB. Increase docking reliability by identifying and incorporating information on binding site packing, key waters, likely side chains movements, and larger conformational changes.

The Cambridge Structural Database System: Eliminate unfavourable conformations and validate binding site interactions by exploiting knowledge derived from over half a million crystal structures.

SuperStar: Constrain dockings using customised knowledge-based maps of interaction hotspots in protein binding sites generated using crystallographic information taken from both the CSD and PDB.