

## REFERENCES

1. Kuntz, I. D. Structure-based strategies for drug design and discovery. *Science* **257**, 1078-1082 (1992).
2. Gohlke, H., Hendlich, M. & Klebe, G. Knowledge-based scoring function to predict proteinligand interactions. *Journal of Molecular Biology* **295**, 337-356 (2000).
3. Verdonk, L., Cole, J. C., Watson, P., Gillet, V. & Willett, P. Superstar: improved knowledge-based interaction fields for protein binding sites. *Journal of Molecular Biology* **307**, 841-859 (2001).
4. Gehlhaar, D. K. et al. Molecular recognition of the inhibitor AG-1343 by HIV-1 protease: conformationally flexible docking by evolutionary programming. *Chemistry & Biology* **2**, 317-324 (1995).
5. Shoichet, B. K., Leach, A. R. & Kuntz, I. D. Ligand solvation in molecular docking. *Proteins: Structure, Function, and Bioinformatics* **34**, 4-6 (1999).
6. Miller, D. W. & Dill, K. A. Ligand binding to proteins: the binding landscape model. *Protein Science* **6**, 2166-2179 (1997).
7. Morris, G. M. et al. Automated docking using a Lamarckian genetic algorithm and empirical binding free energy function. *Journal of Computational Chemistry* **19**, 1639-1662 (1998).
8. Taylor, J. S. & Burnett, R. M. A program for docking flexible molecules. *Proteins: Structure, Function, and Bioinformatics* **41**, 173-191 (2000).
9. Jones, G., Willett, P., Glen, R. C., Leach, A. R. & Taylor, R. Development and validation of a genetic algorithm for flexible docking. *Journal of Molecular Biology* **267**, 727-748 (1997).
10. Sherman, C. J., Ogden, R. C. & Freer, S. T. De novo design of enzyme inhibitors by monte carlo ligand generation. *Journal of Medicinal Chemistry* **38**, 466-472 (1995).
11. Palma, P. N., Krippahl, L., Wampler, J. E., Moura, J. J. G. & BiGGER. A new (soft) docking algorithm for predicting protein interactions. *Proteins: Structure, Function, and Bioinformatics* **39**, 372-384 (2000).
12. Claussen, H., Buning, C., Rarey, M. & Lengauer, T. FlexE: efficient molecular docking considering protein structure variations. *Journal of Molecular Biology* **308**, 377-395 (2001).
13. Leach, A. R. Ligand docking to proteins with discrete side-chain flexibility. *Journal of Molecular Biology* **235**, 345-356 (1994).
14. Osterberg, F., Morris, G. M., Sanner, M. F., Olson, A. J. & Goodsell, D. S. Automated docking to multiple target structures: Incorporation of protein mobility and structural water heterogeneity in autodock. *Proteins: Structure, Function, and Bioinformatics* **46**, 34-40 (2002).
15. Kramer, B., Rarey, M. & Lengauer, T. Evaluation of the flexX incremental construction algorithm for protein-ligand docking. *Proteins: Structure, Function, and Bioinformatics* **37**, 228-241 (1999).
16. Yang, J. M. & Chen, C. C. GEMDOCK: a generic evolutionary method for molecular docking. *Proteins: Structure, Function, and Bioinformatics* **55**, 288-304 (2004).
17. Nissink, J. W. M. C., Hartshorn, M., Verdonk, M. L., Cole, J. C., Taylor, R. A new test set for validating predictions of protein-ligand interaction. *Proteins* **49**, 457 (2002).
18. Lyne, P. D. Structure-based virtual screening: an overview. *Drug Discovery Today* **7**, 1047-1055 (2002).

19. Yang, J. M. & Shen, T. W. A Pharmacophore-Based Evolutionary Approach for Screening Estrogen Receptor Antagonists. *to appear in Congress of Evolutionary Computation (CEC 2004)* (2004).
20. Yang, J.-M., T.-W. Shen, Y.-F. Chen, and Y.-Y. Chiu. An evolutionary approach with pharmacophore-based scoring functions for virtual database screening. *Lecture Notes in Computer Science* (2004).
21. Yang, J. M., Horng, J. T. & Kao, C. Y. A genetic algorithm with adaptive mutations and family competition for training neural networks. *International Journal of Neural Systems* **10**, 333-352 (2000).
22. Yang, J. M. An evolutionary approach for molecular docking. *Lecture Notes in Computer Science* **2724**, 2372-2383 (2003).
23. Yang, J. M. Development and evaluation of a generic evolutionary method for protein-ligand docking. *Journal of Computational Chemistry* **25**, 843-857 (2004).
24. Martin, J. L., Johnson, L. N., Withers, S. G. Comparison of the binding of glucose and glucose 1-phosphate derivatives to T-state glycogen phosphorylase b. *Biochemistry* **29**, 10745 (1990).
25. Mikami, B., Degano, M., Hehre, E. J., Sacchettini, J. C. Crystal structures of soybean beta-amylase reacted with beta-maltose and maltal: active site components and their apparent roles in catalysis. *Biochemistry* **33**, 7779 (1994).
26. LaLonde, J. M., Bernlohr, D. A., Banaszak, L. J. X-ray crystallographic structures of adipocyte lipid-binding protein complexed with palmitate and hexadecanesulfonic acid. Properties of cavity binding sites. *Biochemistry* **33**, 4885 (1994).
27. Williams, S. P., Sigler, P. B. Atomic structure of progesterone complexed with its receptor. *Nature* **393**, 392 (1998).
28. Leslie, A. G. Refined crystal structure of type III chloramphenicol acetyltransferase at 1.75 Å resolution. *J Mol Biol* **213**, 167 (1990).
29. Rahuel, J., Priestle, J. P., Grutter, M. G. The crystal structures of recombinant glycosylated human renin alone and in complex with a transition state analog inhibitor. *J Struct Biol* **107**, 227 (1991).
30. Muller, C. W., Schulz, G. E. Structure of the complex between adenylate kinase from *Escherichia coli* and the inhibitor Ap5A refined at 1.9 Å resolution. A model for a catalytic transition state. *J Mol Biol* **224**, 159 (1992).
31. Hamilton, J. A., Steinrauf, L. K., Braden, B. C., Liepnieks, J., Benson, M. D., Holmgren, G., Sandgren, O., Steen, L. The x-ray crystal structure refinements of normal human transthyretin and the amyloidogenic Val-30-->Met variant to 1.7-Å resolution. *J Biol Chem* **268**, 2416 (1993).
32. Shoichet, B. K., McGovern, S. L., Wei, B. & Irwin, J. Lead discovery using molecular docking. *Current Opinion in Chemical Biology* **6**, 439-446 (2002).
33. Doman, T. N. et al. Molecular docking and high-throughput screening for novel inhibitors of protein tyrosine phosphatase-1B. *Journal of Medicinal Chemistry* **45**, 2213-2221 (2002).
34. Kuntz, I. D., Blaney, J. M., Oatley, S. J., Langridge, R. & Ferrin, T. E. A geometric approach to macromolecular-ligand interactions. *Journal of Molecular Biology* **161**, 269-288 (1982).
35. Ewing, T. J., Makino, S., Skillman, A. G. & Kuntz, I. D. DOCK 4.0: search strategies for automated molecular docking of flexible molecule databases. *Journal of Computer-Aided Molecular Design* **15**, 411-428 (2001).
36. McMartin, C. & Bohacek, R. S. QXP: powerful, rapid computer algorithms for structure-based drug design. *Journal of Computer-Aided Molecular Design* **11**, 333-344

- (1997).
37. Weiner, S. J. et al. A new force field for molecular mechanical simulation of nucleic acids and proteins. *Journal of the American Chemical Society* **106**, 765-784 (1984).
  38. Bissantz, C., Folkers, G. & Rognan, D. Protein-based virtual screening of chemical databases. 1.evaluation of different docking/scoring combinations. *Journal of Medicinal Chemistry* **43**, 4759-4767 (2000).
  39. Stahl, M. & Rarey, M. Detailed analysis of scoring functions for virtual screening. *Journal of Medicinal Chemistry* **44**, 1035-1042 (2001).
  40. Huntigton, J. A. & Baglin, T. P. Targeting thrombin - rational drug design from natural mechanisms. *TRENDS in Pharmacological Sciences* **24**, 589-595 (2003).
  41. Ofosu, F. A. Protease activated receptors 1 and 4 govern the responses of human platelets to thrombin. *Transfusion and Apheresis Science* **28**, 265-268 (2003).
  42. Desai, U. R. New Antithrombin-Based Anticoagulants. *Medicinal Research Reviews* **24**, 151-181 (2004).
  43. Hirsh, J. Oral anticoagulant drugs. *The New England Journal of Medicine* **324**, 1865-1875 (1991).
  44. Hirsh, J. Heparin. *The New England Journal of Medicine* **324**, 1565-1574 (1991).
  45. Banner, D. W. & Hadvary, P. Crystallographic analysis at 3.0-Å resolution of the binding to human thrombin of four active site-directed inhibitors. *Journal of Biological Chemistry* **266**, 20085-20093 (1991).
  46. Baxter, C. A. et al. New approach to molecular docking and its application to virtual screening of chemical databases. *Journal of Chemical Information and Computer Sciences* **40**, 254-262 (2000).
  47. Fisher, L. S. & Guner, O. F. Seeking novel leads through structure-based pharmacophore design. *Journal of The Brazilian Chemical Society* **13**, 777-787 (2002).
  48. Charifson, P. S., Corkery, J. J., Murcko, M. A. & Walters, W. P. Consensus scoring: A method for obtaining improved hit rates from docking databases of three-dimensional structures into proteins. *J Med Chem* **42**, 5100-9 (1999).
  49. Frank, H. D., Shapiro, J. & Taska, I. Methods of Data Fusion in Information Retrieval: Rank vs. Score Combination. *DIMACS Technical Report* **2002**, 58 (2002).
  50. Yang, J. M., Shen, T. W., Chen, Y. F. & Chiu, Y. Y. An evolutionary approach with pharmacophore-based scoring functions for virtual database screening. *Lecture Notes in Computer Science* (2004).
  51. Shen, T. W. in *Institute of Bioinformatics* (National Chiao Tung University, Hsinchu, 2004).
  52. Griffiths, P. D. Progress in the clinical management of herpesvirus infections. *Antiviral Chemistry & Chemotherapy* **6**, 191-209 (1995).
  53. Darby, G. K. In search of the perfect antiviral. *Antiviral Chemistry & Chemotherapy* **6**, 54-63 (1995).
  54. Black, M. E., Newcomb, T. G., Wilson, H. M. & Loeb, L. A. Creation of drug-specific herpes simplex virus type 1 thymidine kinase mutants for gene therapy. *Proceedings of the National Academy of Sciences of the United States of America* **93**, 3525-3529 (1996).
  55. Borrelli, E., Heyman, R., Hsi, M. & Evans, R. M. Targeting of an inducible toxic phenotype in animal cells. *Proceedings of the National Academy of Sciences of the United States of America* **85**, 7572-7576 (1988).
  56. Klazmann, D., Philippon, J., Valery, C. A. & Bensimon, G. Clinical protocol: Gene therapy for glioblastoma in adult patients: Safety and efficacy evaluation of an in situ injection of recombinant retroviruses producing cells carrying the thymidine kinase gene of the herpes simplex type 1 virus, to be followed with the administration of ganciclovir.

- Human Gene Therapy* **7**, 109-126 (1996).
57. Sato, M., Grese, T. A., Dodge, J. A., Bryant, H. U. & Turner, C. H. Emerging therapies for the prevention or treatment of postmenopausal osteoporosis. *Journal of Medicinal Chemistry* **42**, 1-24 (1999).
  58. Torgerson, D. J. HRT and its impact on the menopause, osteoporosis and breast cancer. *Expert Opinion on Pharmacotherapy* **1**, 1163-1169 (2000).
  59. Miller, C. P. SERMs: evolutionary chemistry, revolutionary biology. *Current Pharmaceutical Design* **8**, 2089-2111 (2002).
  60. Dutertre, M. & Smith, C. L. Molecular mechanisms of selective estrogen receptor modulator (SERM) action. *The Journal of Pharmacology and Experimental Therapeutics* **295**, 431-437 (2000).
  61. Maricic, M. & Gluck, O. Review of raloxifene and its clinical applications in osteoporosis. *Expert Opinion on Pharmacotherapy* **3**, 767-775 (2002).
  62. MacGregor, J. I. & Jordan, V. C. Basic guide to the mechanisms of antiestrogen action. *Pharmacological Reviews* **50**, 151-196 (1998).
  63. Gust, R., Keilitz, R. & Schmidt, K. Synthesis, structural evaluation, and estrogen receptor interaction of 2,3-diarylpiperazines. *Journal of Medicinal Chemistry* **45**, 2325-2337 (2002).
  64. Renaud, J. et al. Estrogen receptor modulators: identification and structure-activity relationships of potent ER $\alpha$ -selective tetrahydroisoquinoline ligands. *Journal of Medicinal Chemistry* **46**, 2945-2957 (2003).
  65. van Lipzig, M. M. et al. Prediction of ligand binding affinity and orientation of xenoestrogens to the estrogen receptor by molecular dynamics simulations and the linear interaction energy method. *Journal of Medicinal Chemistry* **47**, 1018-1030 (2004).
  66. Elion, G. B. Nobel lecture in physiology or medicine--1988. The purine path to chemotherapy. *In Vitro Cellular & Developmental Biology* **25**, 321-330 (1989).
  67. Hitchings, G. H., Jr. Nobel lecture in physiology or medicine--1988. Selective inhibitors of dihydrofolate reductase. *In Vitro Cellular & Developmental Biology* **25**, 303-310 (1989).
  68. Wyss, P. C. et al. Novel dihydrofolate reductase inhibitors. Structure-based versus diversity-based library design and high-throughput synthesis and screening. *Journal of Medicinal Chemistry* **46**, 2304-2312 (2003).
  69. Rastelli, G. et al. Docking and database screening reveal new classes of Plasmodium falciparum dihydrofolate reductase inhibitors. *Journal of Computational Chemistry* **46**, 2834-2845 (2003).
  70. Wang, R. & Wang, S. How does consensus scoring work for virtual library screening? An idealized computer experiment. *Journal of Chemical Information and Computer Sciences* **41**, 1422-1426 (2001).
  71. Charifson, P. S., Corkery, J. J., Murcko, M. A. & Walters, W. P. Consensus Scoring: A Method for Obtaining Improved Hit Rates from Docking Databases of Three-Dimensional Structures into Proteins. *Journal of Medicinal Chemistry* **42**, 5100-5109 (1999).
  72. Bissantz, C., Folkers, G. & Rognan, D. Protein-based virtual screening of chemical databases. 1. Evaluation of different docking/scoring combinations. *Journal of Medicinal Chemistry* **43**, 4759-4767 (2000).