

A short list of articles that are referred to in my research from last summer. Basically everything you need to know about the HINT model and water molecule behavior prediction can be gained from this list. It's not entirely exhaustive, but it's close. -Andy

- (1) Cozzini, P.; Fornabaio, M.; Marabotti, A.; Abraham, D. J.; Kellogg, G. E.; Mozzarelli, A. Free energy of ligand binding to protein: evaluation of the contribution of water molecules by computational methods. *Curr. Med. Chem.* 2004, 11, 3093–3118.
- (2) de Graaf, C.; Pospisil, P.; Pos, W.; Folkers, G.; Vermeulen, N. P. Binding mode prediction of cytochrome p450 and thymidine kinase protein-ligand complexes by consideration of water and rescoring in automated docking. *J. Med. Chem.* 2005, 48, 2308–2318.
- (3) Fornabaio, M.; Spyrakis, F.; Mozzarelli, A.; Cozzini, P.; Abraham, D. J.; Kellogg, G. E. Simple, intuitive calculations of free energy of binding for protein-ligand complexes. 3. The free energy contribution of structural water molecules in HIV-1 protease complexes. *J. Med. Chem.* 2004, 47, 4507–4516.
- (4) Garcia-Sosa, A. T.; Firth-Clark, S.; Mancera, R. L. Including tightly-bound water molecules in de novo drug design. Exemplification through the in silico generation of poly(ADP-ribose)polymerase ligands. *J. Chem. Inf. Model.* 2005, 45, 624–633.
- (5) Li, Z.; Lazaridis, T. Water at biomolecular binding interfaces. *Phys. Chem. Chem. Phys.* 2007, 9, 573–581.
- (6) Mancera, R. L. De novo ligand design with explicit water molecules: an application to bacterial neuraminidase. *J. Comput.-Aided Mol. Des.* 2002, 16, 479–499.
- (7) Rarey, M.; Kramer, B.; Lengauer, T. The particle concept: placing discrete water molecules during protein-ligand docking predictions. *Proteins* 1999, 34, 17–28.
- (8) Wang, J.; Chan, S. L.; Ramnarayan, K. Structure-based prediction of free energy changes of binding of PTP1B inhibitors. *J. Comput.-Aided Mol. Des.* 2003, 17, 495–513.
- (9) Klebe, G. Virtual ligand screening: strategies, perspectives and limitations. *Drug DiscoVery Today* 2006, 11, 580–594.
- (10) Lu, Y.; Wang, R.; Yang, C. Y.; Wang, S. Analysis of ligand-bound water molecules in high-resolution crystal structures of protein-ligand complexes. *J. Chem. Inf. Model.* 2007, 47, 668–675.
- (11) Garcia-Sosa, A. T.; Mancera, R. L.; Dean, P. M. WaterScore: a novel method for distinguishing between bound and displaceable water molecules in the crystal structure of the binding site of protein-ligand complexes. *J. Mol. Model.* 2003, 9, 172–182.
- (12) Raymer, M. L.; Sanschagrin, P. C.; Punch, W. F.; Venkataraman, S.; Goodman, E. D.; Kuhn, L. A. Predicting conserved water-mediated and polar ligand interactions in proteins using a K-nearest-neighbors genetic algorithm. *J. Mol. Biol.* 1997, 265, 445–464.
- (13) Barillari, C.; Taylor, J.; Viner, R.; Essex, J. W. Classification of water

- molecules in protein binding sites. *J. Am. Chem. Soc.* 2007, 129, 2577–2587.
- (14) Li, Z.; Lazaridis, T. Thermodynamic contributions of the ordered water molecule in HIV-1 protease. *J. Am. Chem. Soc.* 2003, 125, 6636–6637.
- (15) Lu, Y.; Yang, C. Y.; Wang, S. Binding free energy contributions of interfacial waters in HIV-1 protease/inhibitor complexes. *J. Am. Chem. Soc.* 2006, 128, 11830–11839.
- (16) Lam, P. Y.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bachelier, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Chang, C. H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Ericksonviitanen, S. Rational design of potent, bioavailable, nonpeptide cyclic ureas as HIV protease inhibitors. *Science* 1994, 263, 380–384.
- (17) Coburn, C. A.; Stachel, S. J.; Li, Y. M.; Rush, D. M.; Steele, T. G.; Chen-Dodson, E.; Holloway, M. K.; Xu, M.; Huang, Q.; Lai, M. T.; DiMuzio, J.; Crouthamel, M. C.; Shi, X. P.; Sardana, V.; Chen, Z. G.; Munshi, S.; Kuo, L.; Makara, G. M.; Annis, D. A.; Tadikonda, P. K.; Nash, H. M.; Vacca, J. P.; Wang, T. Identification of a small molecule nonpeptide active site beta-secretase inhibitor that displays a nontraditional binding mode for aspartyl proteases. *J. Med. Chem.* 2004, 47, 6117–6119.
- (18) Ladbury, J. E. Just add water! The effect of water on the specificity of protein-ligand binding sites and its potential application to drug design. *Chem. Biol.* 1996, 3, 973–980.
- (19) Jones, G.; Willett, P.; Glen, R. C.; Leach, A. R.; Taylor, R. Development and validation of a genetic algorithm for flexible docking. *J. Mol. Biol.* 1997, 267, 727–748.
- (20) Verdonk, M. L.; Chessari, G.; Cole, J. C.; Hartshorn, M. J.; Murray, C. W.; Nissink, J. W.; Taylor, R. D.; Taylor, R. Modeling water molecules in protein-ligand docking using GOLD. *J. Med. Chem.* 2005, 48, 6504–6515.
- (21) Kellogg, G. E.; Abraham, D. J. Hydrophobicity: is LogP(o/w) more than the sum of its parts? *Eur. J. Med. Chem.* 2000, 35, 651–661.
- (22) Amadasi, A.; Spyralis, F.; Cozzini, P.; Abraham, D. J.; Kellogg, G. E.; Mozzarelli, A. Mapping the energetics of water-protein and water-ligand interactions with the “natural” HINT forcefield: predictive tools for characterizing the roles of water in biomolecules. *J. Mol. Biol.* 2006, 358, 289–309.
- (23) Burnett, J. C.; Botti, P.; Abraham, D. J.; Kellogg, G. E. Computationally accessible method for estimating free energy changes resulting from site-specific mutations of biomolecules: systematic model building and structural/hydrophobic analysis of deoxy and oxy hemoglobins. *Proteins* 2001, 42, 355–377.
- (24) Cozzini, P.; Fornabaio, M.; Marabotti, A.; Abraham, D. J.; Kellogg, G. E.; Mozzarelli, A. Simple, intuitive calculations of free energy of binding for protein-ligand complexes. 1. Models without explicit

- constrained water. *J. Med. Chem.* 2002, 45, 2469–2483.
- (25) Spyrakis, F.; Cozzini, P.; Bertoli, C.; Marabotti, A.; Kellogg, G. E.; Mozzarelli, A. Energetics of the protein-DNA-water interaction. *BMC Struct. Biol.* 2007, 7, 4.
- (26) Spyrakis, F.; Fornabai, M.; Cozzini, P.; Mozzarelli, A.; Abraham, D. J.; Kellogg, G. E. Computational titration analysis of a multiprotic HIV-1 protease-ligand complex. *J. Am. Chem. Soc.* 2004, 126, 11764–11765.
- (27) Kellogg, G. E.; Chen, D. L. The importance of being exhaustive. Optimization of bridging structural water molecules and water networks in models of biological systems. *Chem. Biodiversity* 2004, 1, 98–105.
- (28) Carugo, O.; Bordo, D. How many water molecules can be detected by protein crystallography? *Acta Crystallogr., Sect. D: Biol. Crystallogr.* 1999, 55, 479–483.
- (29) Davis, A. M.; Teague, S. J.; Kleywegt, G. J. Application and limitations of X-ray crystallographic data in structure-based ligand and drug design. *Angew. Chem., Int. Ed.* 2003, 42, 2718–2736.
- (30) Levitt, M.; Park, B. H. Water: now you see it, now you don't. *Structure* 1993, 1, 223–236.
- (31) Goodford, P. J. A computational procedure for determining energetically favorable binding sites on biologically important macromolecules. *J. Med. Chem.* 1985, 28, 849–857.
- (32) Dunitz, J. D. The entropic cost of bound waters in crystals and biomolecules. *Science* 1994, 264, 670.
- (33) Vargas, R.; Garza, J.; Dixon, D. A.; Benjamin, P. H. How strong is the CR-H ··· OdC hydrogen bond? *J. Am. Chem. Soc.* 2000, 122, 4750–4755.
- (34) Pillai, B.; Kannan, K. K.; Hosur, M. V. 1.9 Å X-ray study shows closed flap conformation in crystals of tethered HIV-1 PR. *Proteins* 2001, 43, 57–64.
- (35) Withlow, M.; Howard, A. J.; Stewart, D.; Hardman, K. D.; Kuyper, L. F.; Baccanari, D. P.; Fling, M. E.; Tansik, R. L. X-ray crystallographic studies of *Candida albicans* dihydrofolate reductase. High resolution structures of the holoenzyme and an inhibited ternary complex. *J. Biol. Chem.* 1997, 272, 30289–30298.