

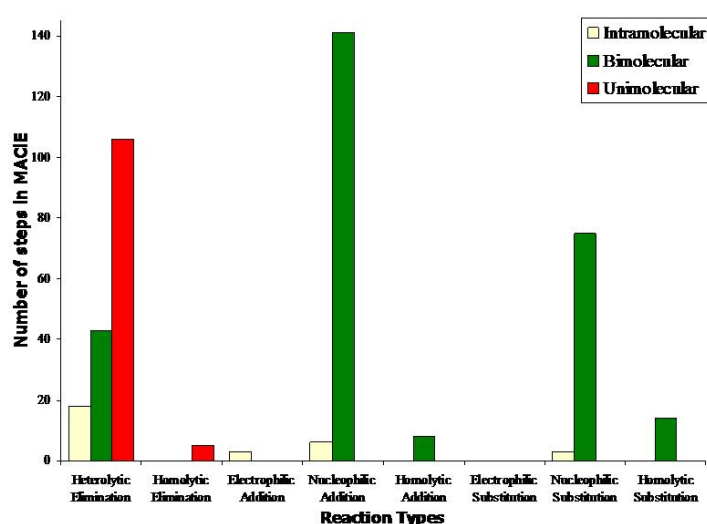
Dr John Mitchell Reader in Translational Biology

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Research Interests: structural bioinformatics, enzyme reaction mechanisms, chemoinformatics, solubility, machine learning, computational toxicology.



The interface between biology and chemistry is fertile ground for the development of new computational techniques. Yet it is still hard to predict protein-ligand binding, model protein folding or design effective pharmaceutical products.



Enzyme-catalysed reactions are ubiquitous and essential to the chemistry of life. Structures, gene sequences, mechanisms, metabolic pathways and kinetic data are currently spread between many different databases and throughout the literature. We have created MACIE, the world's first comprehensive electronic database of the chemical mechanisms of enzymatic reactions. We are using MACIE to investigate fundamental questions about the chemistry of enzymes' functions, their evolution, and their substrate specificity. The Figure shows the reaction types in MACIE.

Improving the prediction of **solubility** is essential to reduce the current unacceptable attrition rate in drug development. We are developing methods to predict aqueous solubility for drug-like molecules, and hope to move on to study its dependence on factors like hydrophobicity and crystal polymorphism. We have developed a number of predictive methods for solubility, of which the most successful is based on a Random Forest of decision trees. We have also used computational chemistry to calculate the various energy terms associated with solvation, completing a thermodynamic cycle. This work spans quantum chemistry, molecular simulation, QSPR and chemoinformatics.

Selected Publications

1. F Nigsch & JBO Mitchell, Toxicological Relationships Between Proteins Obtained from Protein Target Predictions of Large Toxicity Databases, *Toxicology and Applied Pharmacology*, (2008), 231, 225-234
2. DS Palmer, A Llinàs, I Morao, GM Day, JM Goodman, RC Glen & JBO Mitchell, Predicting Intrinsic Aqueous Solubility by a Thermodynamic Cycle, *Molecular Pharmaceutics*, (2008), 5, 266-279
3. NM O'Boyle, GL Holliday, DE Almonacid & JBO Mitchell, Using Reaction Mechanism to Measure Enzyme Similarity, *Journal of Molecular Biology*, (2007), 368, 1484-1499
4. GL Holliday, DE Almonacid, JBO Mitchell & JM Thornton, The Chemistry of Protein Catalysis, *Journal of Molecular Biology*, (2007), 372, 1261-1277
5. DS Palmer, NM O'Boyle, R C Glen & JBO Mitchell, Random Forest Models to Predict Aqueous Solubility, *Journal of Chemical Information and Modeling*, (2007), 47, 150-158