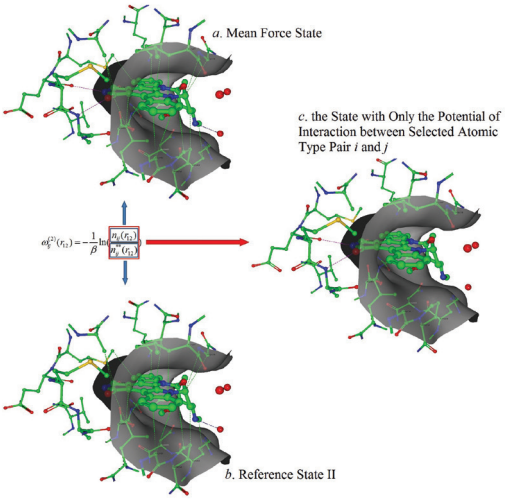
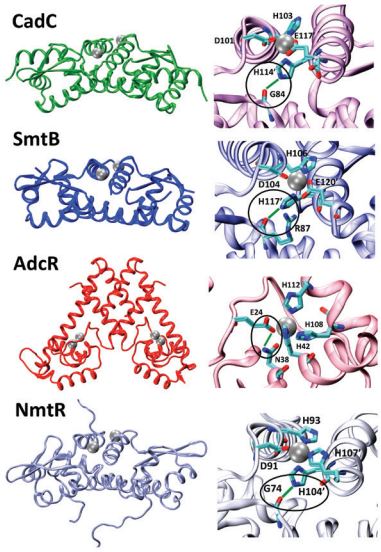
RESEARCH AT THE INTERFACE

between the computational sciences and biology is our group focus. We work on a number of problems and collaborate with experimentalists at every opportunity. Research areas of most interest include computer-aided drug design (CADD), the role potential function error plays in drug design and protein folding, metalloenzymes and metal ion homeostasis, development and application of linear-scaling quantum mechanical methods to biological problems and NMR and X-ray structure refinement using quantum mechanical methods. For further details go to the group web page at ***http://merzgroup.org***.

In the structure-based drug design area we are interested in developing novel tools to predict the binding affinity of ligands for a given receptor. Along these lines we developed a novel knowledge-based protein-ligand scoring function that employs a new definition for the reference state (see the Figure), allowing us to relate a statistical potential to a Lennard-Jones (LJ) potential. In this way, the LJ potential parameters were generated from protein-ligand complex structural data contained in the PDB. Forty-nine types of atomic pairwise interactions were derived using this method, which we call the knowledge-based and empirical combined scoring algorithm (KECSA). Validation results illustrate that KECSA shows improved performance in all test sets when compared with other scoring methods especially in its ability to minimize the RMSE.



A protein-ligand structural illustration (using PDBID 1xbc) of how the KECSA statistical potential is modeled. The protein binding site is shown as a grey surface with the ligand located within the binding site surrounded by protein residues which it makes contacts with. The pink dashed lines indicate interactions between certain atom pair types i *and* j*, (*i.e. *carbonyl oxygen with amine nitrogens in this example) which are defined as "selected interactions" in this manuscript. Green dashed lines indicate all other non-covalent interactions between the protein and ligand atoms in the binding pocket, defined as "background interactions". (a) In the mean force state, the system is filled with all types of interactions. (b) The reference state II contains all the background interactions. (c) Removing all the background interactions from total interactions results in a state with only the selected interactions for each* i *and* j *combination.*



Protein Structure and zinc coordination in CadC (1U2W), SmtB (1R22) AdcR (3TGN) and NmtR (computational model) transcriptional regulators. Zinc ions are shown as silver spheres and the hydrogen bonds are shown with a green line.

Metalloenzymes carry out a myriad of biological functions and we have a long-term interest in modeling the structure and function of proteins involving metal ion catalysis or homeostasis. A recent publication illustrates an example of the study of transition metal homeostasis. A metal-mediated interprotomer hydrogen bond has been implicated in the allosteric mechanism of DNA operator binding in several metal-sensing proteins. Using computational methods, we investigated the energetics of such zinc-mediated interactions in members of the ArsR/SmtB family of proteins (CzrA, SmtB, CadC and NmtR) and the MarR family zinc-uptake repressor AdcR, each of which feature similar interactions, but in sites that differ widely in their allosteric responsiveness. We provided novel structural insight into previously uncharacterized allosteric forms of these proteins using computational methodologies. We find this metal-mediated interaction to be significantly stronger (~8 kcal/mol) at functional allosteric metal binding sites compared to a non-responsive site (CadC) and the apo-proteins. Simulations of the apo-proteins further revealed that the high interaction energy works to overcome the considerable disorder at these hydrogen-bonding sites and functions as a "switch" to lock in a weak DNA-binding conformation once metal is bound. These findings suggested a globally conserved functional role of metal-mediated second-coordination shell hydrogen bonds at allosterically responsive sites in zinc-sensing transcription regulators.

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Selected Publications

The Effects of Computational Modeling Errors on the Estimation of Statistical Mechanical Variables, J. C. Faver; W. Yang; K. M. Merz, Jr., *J. Chem. Theory and Comput.* **2012**, *8*, 3769–3776.

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Energetics of Zinc-Mediated Interactions in the Allosteric Pathways of Metal Sensor Proteins, D. K. Chakravorty; T. M. Parker; A. J. Guerro; C. D. Sherrill; D. P. Giedroc, K. M. Merz, Jr., *J. Am Chem. Soc.* **2013**, *135*, 30–33.

Conformational analysis and parallel QM/MM X-ray refinement of protein bound anti-Alzheimer drug donepezil, Z. Fu; X. Li; Y. Miao; K. M. Merz, Jr., *J. Chem. Theory and Comput.* **2013**, *9*, 1686-1693.

Development of the Knowledge-based & Empirical Combined Scoring Algorithm (KECSA) to Score Protein-Ligand Interactions, Z. Zheng; K. M. Merz, Jr., *J. Chem. Inf. Model.* **2013**, *53*, 1073–1083.