Dr. Michael J. Schnieders

Departments of Biomedical Engineering and Biochemistry
The University of Iowa
51 Newton Rd., 4-403 Bowen Science Building
Iowa City, IA 52358
(650) 995-3526
Michael-schnieders@uiowa.edu
http://ffx.kenai.com

EDUCATION

Postdoctoral Fellow, Biomedical Engineering, 2011-2012
The University of Texas, Austin, TX
Advisor: Prof. Pengyu Ren

Postdoctoral Fellow, Chemistry, 2007–2010
Stanford University, Stanford, CA
Advisor: Prof. Vijay S. Pande

Doctorate, Biomedical Engineering, 2007
Washington University in St. Louis, St. Louis, MO
Dissertation: The Theory and Effect of Solvent Environment on Biomolecules
Advisor: Prof. Jay W. Ponder

Bachelor of Science in Engineering with High Distinction, Biomedical Engineering, 1999
The University of Iowa, Iowa City, IA
Advisors: Prof. Thomas D. Brown (1997 - 1999)
Prof. Joseph M. Reinhardt (Summer 1999)
GPA: 3.9

HONORS

Burroughs Wellcome Fund Travel Award, The University of Texas at Austin, 2012
Best Poster Award, Electron Density and Chemical Bonding Gordon Research Conf., Stanford University, 2010
Selected for NIH Training Grant, Washington University in St. Louis, 2004
Grace Norman Fellowship, Washington University in St. Louis, 2001
Rhodes Dunlap Scholarship, The University of Iowa, 1998
National Barry Goldwater Excellence in Education Scholarship, The University of Iowa, 1997
Howard Hughes Research Assistantship, The University of Iowa, 1997
Alpha Eta Mu Beta Honor Society, Top 20% of BME Class, The University of Iowa, 1997
Howard Hughes Teaching Assistant, The University of Iowa, 1997
Paul D. Scholz Memorial Scholarship, The University of Iowa, 1996
Tau Beta Pi Honor Society, Top 12.5% of Engineering Class, The University of Iowa, 1996
Stebler Scholarship, The University of Iowa, 1995

RESEARCH INTERESTS

My research interests are focused on the molecular biophysics theory and high performance computational algorithms that are essential to reducing the time and cost of engineering new pharmaceuticals. A complementary goal is to understand patient specific responses to pharmaceuticals by integrating genetic information and molecular phenotypes.

1. Next Generation Theory and Tools for Biomolecular X-ray Crystallography

   - Structure-based drug design starts from protein-ligand models derived from refinement of X-ray crystallography diffraction data. For the first time, we have incorporated rigorous electrostatics algorithms into X-ray refinement, which has produced leading biomolecular structural models in terms of improved agreements with both experimental data (i.e. lower R/R_{free}) and with prior chemical knowledge (i.e. hydrogen-bonding).

2. Rational Drug Design and Personalized Medicine via Computation of Protein-Ligand Binding Affinity

   - A next step in structure-based drug design is the identification of lead compounds that exhibit high affinity and specificity for their biomolecular target. We have contributed leading continuum electrostatic models that strike a balance between accuracy and efficiency for the treatment of the (de)solvation forces that drive protein-ligand binding.

3. Computational Thermodynamics of Organic Materials

   - A final step in rational drug design is formulation of the compound for optimal drug delivery. For the first time, we have demonstrated the ability to compute the thermodynamics of organic crystals from first principles using molecular dynamics simulations. This opens to the door to a limitless range of applications including the prediction and engineering of drug solubility.

4. Director: *Force Field X* High Performance Molecular Biophysics Software Project

   - Our *Force Field X* computer code is an emerging tool for:
     1. Refinement of biomolecular structures from X-ray diffraction experiments.
     2. Prediction of protein-ligand binding affinity.
     3. Computational thermodynamics of organic materials.

   - *Force Field X* is disseminated to the community free of charge, with source code, under the GPL v. 3 license. (http://ffx.kenai.com)

TEACHING INTERESTS

Undergraduate
- Thermodynamics, Biochemistry, Biomaterials, Computer Science

Graduate
- Structural Biology, Computational (Bio)Chemistry, Computational (Bio)Materials, Statistical Mechanics

RESEARCH EXPERIENCE

Assistant Professor, 2012-present
Departments of Biomedical Engineering and Biochemistry, The University of Iowa, IA

Postdoctoral Fellow, 2011-2012
Laboratory of Professor Pengyu Ren
Department of Biomedical Engineering, The University of Texas, Austin, TX

The goal of my work with Prof. Ren has been to combine the polarizable AMOEBA force field with advanced molecular dynamics free energy algorithms pioneered by Prof. Wei Yang at Florida State University in order to compute protein-ligand binding affinity and organic crystal thermodynamics as efficiently as possible within our *Force Field X* code. Our project was selected for an oral presentation at the 2012 Biophysical Society Conference and is partially supported by a 2012 Burroughs Wellcome Fund Travel Award.

- Reviewed *Computational insights for the discovery of non-ATP competitive inhibitors of MAP kinases* (with Prof. Kevin Dalby).[1]

- **Completed the first computational predictions of drug solubility from first principles atomic resolution molecular dynamics simulations using *Force Field X*. This demonstrates our ability to explain the thermodynamics of organic crystals and opens the door to their rational design in the future** (with Prof. Wei Yang).[2]

- Contributed to the review article *Biomolecular electrostatics and solvation: a computational perspective* (with Nathan Baker).[3]

- Contributed to *Assessment of protein structure refinement in CASP9* by comparing submitted structures against X-ray diffraction data (with Profs. Ken Dill and Matthew Jacobson).[5]

- Demonstrated that biomolecular structural models from AMOEBA-assisted X-ray refinement with *Force Field X* agree more closely with both the experimental data and what is known about molecular physics than previous generation approaches.[7]

Postdoctoral Fellow, 2007–2010
Laboratory of Professor Vijay S. Pande
Department of Chemistry, Stanford University, Palo Alto, CA

Macromolecular X-ray crystallography is a critical experimental method for obtaining atomic resolution models for rational structure-based drug design. **Our work has resulted in new theory and tools that deliver leading protein-ligand structural models.** This project was chosen for an oral presentation and received the Best Poster Award at the 2010 Electron Density and Chemical Bonding Gordon Research Conference.

- Derived, implemented and parallelized space group support for particle-mesh Ewald (PME) electrostatics that scales up to any sized biomolecular X-ray crystallography data set in the Protein Databank within our *Force Field X* high performance molecular biophysics engine.[4]

- Derived and implemented a biomolecular electron density model using Cartesian Gaussian multipoles and applied this model to study the hydrogen bonding networks of enzymes (with Prof. Axel Brunger).[9,12]

- Validated the AMOEBA force field against high-resolution X-ray crystallography data sets (with Profs. Jay Ponder, Teresa Head-Gordon and Martin Head-Gordon).[8]

- Provided theoretical support to *Remeasuring the Double Helix* (with Prof. Pehr Harbury).[13]

- Contributed to *Assessment of the protein-structure refinement category in CASP8* by comparing submitted structures against X-ray diffraction data (with Profs. Ken Dill and Matthew Jacobson).[14]

Predoctoral Fellow, 2001–2007
Laboratory of Professor Jay W. Ponder
Department of Biomedical Engineering, Washington University in St. Louis, St. Louis, MO

The solvation of biomolecules drives their folding and function. To efficiently simulate proteins and their interactions with drugs or other proteins, my thesis work with Prof. Ponder described how to replace atomic resolution solvent details with a polarizable continuum.

- Derived and implemented a numerical continuum electrostatics model for the polarizable multipole AMOEBA force field based on the linearized Poisson-Boltzmann equation (with Nathan Baker).[17]

- Derived and implemented an analytic approximation to solving the linearized Poisson-Boltzmann equation that extends the generalized Born model to polarizable multipoles, termed generalized Kirkwood (GK).[16] **GK is becoming a leading analytic continuum electrostatics solution for the study of protein folding and for protein-ligand binding calculations during rational drug design**.[15]

- Derived, implemented and parameterized complete implicit solvent models for the AMOEBA force field based on Poisson-Boltzmann and GK electrostatics.

Research Assistant, Spring 2001
Laboratory of Professor Jay W. Ponder
Department of Biochemistry and Molecular Biophysics, Washington University in St. Louis, St. Louis, MO

- Continued to work on the *Force Field X* molecular biophysics engine.

Independent Study, 2000

- Began writing the *Force Field X* molecular biophysics engine as a precursor to contacting Prof. Jay W. Ponder at Washington U. in St. Louis.

- Pursued independent study and subsequent examination to achieve Sun Microsystems, Inc. Certification on the Java™ Platform at the Programmer level.

Research Assistant, Summer 1999
Laboratory of Joseph M. Reinhardt
Department of Biomedical Engineering, The University of Iowa, Iowa City, IA

- Contributed to porting a C++ based image analysis library from Unix to Windows.

Howard Hughes Research Assistantship / Barry Goldwater Scholarship, 1997–1999
Laboratory of Professor Thomas D. Brown
Orthopaedic Biomechanics Laboratory, The University of Iowa, Iowa City, IA

- Applied and was selected for the Howard Hughes Research Assistantship program administered within The U. of Iowa Department of Biology.

- Studied the accuracy of a surgical drill guide for placing grafts or pins through the femoral neck and into the femoral head.[18,19]

- Quantified the mechanical properties of osteonecrotic femoral heads and a composite fiberglass surrogate.

Research Assistant, 1996–1997
Supervised by Dr. James Martin
Ponseti Biochemistry and Cell Biology Laboratory, The University of Iowa, Iowa City, IA

- Applied image analysis techniques to measure staining of IGF-1 in articular cartilage from confocal microscopy images.

- While working with Dr. Martin, I applied for independent support via a Howard Hughes Research Assistantship through The University of Iowa Biology Department. The application process required choosing a mentor registered with the program, which is how I met Prof. Thomas D. Brown.

Laboratory Technician, 1995–1996
Supervised by Kenneth C. Moore
Central Microscopy Research Facility, The University of Iowa, Iowa City, IA

- Maintained equipment and reagents for processing of specimens.

- Supported researchers in their use of SEM, TEM, AFM and Confocal microscopy techniques.

- Pursued opportunities for increased independent work in the Ponseti Biochemistry and Cell Biology Laboratory following an introduction by Kenneth Moore to Dr. Joseph Buckwalter.

TEACHING EXPERIENCE

Teaching Assistant, 2004–2007
Department of Biochemistry and Molecular Biophysics, Washington University in St. Louis, St. Louis, MO

- Instructed students in the use of both the *TINKER* and *Force Field X* programs during an annual Computational Biochemistry course.

Volunteer Tutor, 2003
Department of Biochemistry and Molecular Biophysics, Washington University in St. Louis, St. Louis, MO

- Recruited by the Department of Biochemistry and Molecular Biophysics to tutor with pay a fellow graduate student enrolled in an advanced course in Statistical Thermodynamics. The student needed to receive a B or higher to meet Ph.D. requirements. Although I declined payment, I tutored the student through successful completion of the course.

Teaching Assistant, 1998
Department of Electrical and Computer Engineering, The University of Iowa, Iowa City, IA

- Recruited to be a TA for the course Computers in Engineering.

- Led two lab sections per week while also grading assignments and tests. Students implemented C programs to control hardware for three different applications: an oscilloscope and its signals, traffic lights and a memory game.

Howard Hughes Teaching Assistant, 1997
Department of Biology, The University of Iowa, Iowa City, IA

- Applied and was selected for the Howard Hughes Teaching Assistant program administered within The University of Iowa Department of Biology.

- Led two study sections per week for an undergraduate introductory biology course. Attendance was not required and, therefore, usually consisted of students who were motivated to discuss current lecture material that they found particularly challenging or thought provoking.

PUBLICATIONS

Only accepted, rigorously peer reviewed articles are listed.

1. Schnieders, M. J., Kaoud, T. S., Yan, C., Dalby, K. N., and Ren, P. (2012) Computational insights for the discovery of non-ATP competitive inhibitors of MAP kinases, *Current Pharmaceutical Design 18*, 1173-1185.

2. Schnieders, M. J., Baltrusaitis, J., Shi, Y., Chattree, G., Zheng, L., Yang, W., and Ren, P. (2012) The Structure, Thermodynamics, and Solubility of Organic Crystals from Simulation with a Polarizable Force Field, *Journal of Chemical Theory and Computation 8*, 1721-1736.

3. Ren, P., Chun, J., Thomas, D. G., Schnieders, M. J., Marucho, M., Zhang, J., and Baker, N. A. (2012) Biomolecular electrostatics and solvation: a computational perspective, *Quarterly Reviews of Biophysics 45 (To Appear)*.

4. Schnieders, M. J., Fenn, T. D., and Pande, V. S. (2011) Polarizable atomic multipole X-ray refinement: Particle mesh Ewald electrostatics for macromolecular crystals, *Journal of Chemical Theory and Computation 7*, 1141-1156.

5. MacCallum, J. L., Pérez, A., Schnieders, M. J., Hua, L., Jacobson, M. P., and Dill, K. A. (2011) Assessment of protein structure refinement in CASP9, *Proteins: Structure, Function, and Bioinformatics 79*, 74-90.

6. Fenn, T. D., Schnieders, M. J., Mustyakimov, M., Wu, C., Langan, P., Pande, V. S., and Brunger, A. T. (2011) Reintroducing electrostatics into macromolecular crystallographic refinement: Application to neutron crystallography and DNA hydration, *Structure 19*, 523-533.

7. Fenn, T. D., and Schnieders, M. J. (2011) Polarizable atomic multipole X-ray refinement: weighting schemes for macromolecular diffraction, *Acta Crystallographica Section D 67*, 957-965.

8. Ponder, J. W., Wu, C., Ren, P., Pande, V. S., Chodera, J. D., Schnieders, M. J., Haque, I., Mobley, D. L., Lambrecht, D. S., DiStasio, R. A., Head-Gordon, M., Clark, G. N. I., Johnson, M. E., and Head-Gordon, T. (2010) Current status of the AMOEBA polarizable force field, *Journal of Physical Chemistry B 114*, 2549-2564.

9. Fenn*, T. D., Schnieders*, M. J., Brunger, A. T., and Pande, V. S. (2010) Polarizable atomic multipole X-ray refinement: hydration geometry and application to macromolecules, *Biophysical Journal 98*, 2984-2992 (*joint first authors).

10. Fenn, T. D., Schnieders, M. J., and Brunger, A. T. (2010) A smooth and differentiable bulk-solvent model for macromolecular diffraction, *Acta Crystallographica Section D 66*, 1024-1031.

11. Shi, Y., Jiao, D., Schnieders, M. J., and Pengyu, R. (2009) Trypsin-ligand binding free energy calculation with AMOEBA, In *Engineering in Medicine and Biology Society. EMBC. Annual International Conference of the IEEE*, pp 2328-2331.

12. Schnieders, M. J., Fenn, T. D., Pande, V. S., and Brunger, A. T. (2009) Polarizable atomic multipole X-ray refinement: Application to peptide crystals, *Acta Crystallographica Section D 65*, 952-965.

13. Mathew-Fenn, R. S., Das, R., Fenn, T. D., Schnieders, M. J., and Harbury, P. A. B. (2009) Response to comment on "Remeasuring the double helix", *Science 325*, 538.

14. MacCallum, J. L., Hua, L., Schnieders, M. J., Pande, V. S., Jacobson, M. P., and Dill, K. A. (2009) Assessment of the protein-structure refinement category in CASP8, *Proteins: Structure, Function, and Bioinformatics 77*, 66-80.

15. Jiao, D., Zhang, J. J., Duke, R. E., Li, G. H., Schnieders, M. J., and Ren, P. (2009) Trypsin-ligand binding free energies from explicit and implicit solvent simulations with a polarizable potential, *J. Comput. Chem. 30*, 1701-1711.

16. Schnieders, M. J., and Ponder, J. W. (2007) Polarizable atomic multipole solutes in a generalized Kirkwood continuum, *Journal of Chemical Theory and Computation 3*, 2083-2097.

17. Schnieders, M. J., Baker, N. A., Ren, P., and Ponder, J. W. (2007) Polarizable atomic multipole solutes in a Poisson-Boltzmann continuum, *Journal of Chemical Physics 126*, 1-21.

18. Anderson, D. A., Schnieders, M. J., Heiner, A. D., Pedersen, D. R., Brown, T. D., and Brand, R. A. (1999) A surgical guide to accurately place pins or nails within the femoral head, *Journal of Musculoskeletal Research 3*, 233-237.

19. Schnieders, M. J., Dave, S. B., Morrow, D. E., Heiner, A. D., Pedersen, D. R., and Brown, T. D. (1997) Assessing the accuracy of a prototype drill guide for fibular graft placement in femoral head necrosis, *Iowa Orthopaedic Journal 17*, 58-63.