BIOGRAPHICAL SKETCH
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NAME: David L. Mobley

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POSITION TITLE: Associate Professor, Departments of Pharmaceutical Sciences and Chemistry

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of California, Davis	B.S.	06/2000	Physics
University of California, Davis	M.S.	06/2002	Physics
University of California, Davis	Ph.D.	06/2004	Physics
University of California, San Francisco	Postdoctoral	2004-2008	Comp. chem./modeling

A. PERSONAL STATEMENT

My research focuses specifically on using molecular simulations to understand and predict molecular interactions, solvation, solubility, and other properties relating to molecular design. A major goal is enabling molecular design for applications in drug discovery, bioengineering and other areas. I also have major interests – and an extensive background – in using blind prediction challenges to drive progress in my own work and in the field. The present project focuses on developing model systems of varying complexity to span between physical modeling exercises which are tractable with today's methods and pharmaceutical applications which are, in some cases, far too complex; generating experimental data; and running blind challenges to use this data to advance predictive modeling.

My group is particularly well suited to this task, given our extensive experience with predictive modeling and blind challenges and long history with the SAMPL challenge itself. In my postdoctoral work with Ken Dill, I participated in informal blind predictive challenges with experimentalists in the Shoichet lab, where I predicted binding free energies and the Shoichet lab separated measured the same. This led me to early see the value of blind tests for method development, as they involve much more careful planning and analysis of protocols than do retrospective tests, and a great deal more is typically learned. This early involvement in blind challenges led to my participation in an OpenEye CUP blind prediction challenge on hydration free energies which we now refer to as SAMPL0, and subsequently I participated in every SAMPL challenge through SAMPL3 (where I also oversaw the hydration free energy component of the challenger), when SAMPL transitioned out of being run by OpenEye. At that point, I took over running SAMPL, running SAMPL4 largely within my group with help on host-guest systems from Michael Gilson (see support letter). Subsequently, I worked with John Chodera to coordinate experimental work at Genentech for log D data for SAMPL5, and with Mike Gilson to bring in host-guest measurements by Bruce Gibb and Lyle Isaacs. So my role in SAMPL0-3 was as a participant and partial organizer, and in SAMPL4-5 I've been the primary organizer with help from others.

In addition to my work on SAMPL, I have extensive experience applying free energy calculations and physical methods both to predicting binding and to prediction of physical properties, driving my group's role in performing reference calculations (Aim 4) for the challenges proposed in this work. My group consists of a postdoctoral researcher, eight graduate students, and several undergraduates, and we are actively involved in methodology and application of free energy calculations to biomolecular binding, drug discovery, and prediction

of solvation and solubility. We also have a major force field effort underway, currently in its early stages, which will have overlap with the science covered in this proposal.

The four publications below highlight our specific expertise for this project and focus on our role in, and the community's lessons learned from, the past two SAMPL challenges, of which I was an organizer:

    a. Rustenburg, A.S, Dancer, J., Lin, B., Feng, J.A., Ortwine, D.F., **Mobley, D.L**., and Chodera, J.D**.** Measuring experimental cyclohexane-water distribution coefficients for the SAMPL5 challenge. *Journal of Computer Aided Molecular Design,* in press.

    b. **D. L. Mobley,** S. Liu, N. M. Lim, K. L. Wymer, A. L. Perryman, S. Forli, N. Deng, J. Su, K. Branson, and A. J. Olson, "Blind prediction of HIV integrase binding from the SAMPL4 challenge", *J. Comput. Aided Mol. Design* 28(4):327-345 (2014). PMCID PMC4331050.

    c. H. S. Muddana, A. T. Fenley, **D. L. Mobley**, and M. K. Gilson, "The SAMPL4 host-guest blind prediction challenge: an overview", *J. Comput. Aided Mol. Design* 28(4):305-317 (2014). PMCID PMC4053502

    d. **D. L. Mobley,** K. L. Wymer, and N. M. Lim, "Blind prediction of solvation free energies from the SAMPL4 challenge", *J. Comput. Aided Mol. Design* **28**:135-150 (2014). PMCID PMC4006301

B. POSITIONS AND HONORS

Positions and Employment
06/2004 – 12/2007	Postdoctoral researcher, Dept. of Pharm. Chem., University of California, San Francisco
12/2007 – 06/2008	Chief Science Officer, Simprota Corporation, San Francisco, CA
06/2008 – 08/2008	Postdoctoral researcher, Dept. of Pharm. Chem., University of California, San Francisco
08/2008 – 06/2012	Assistant Professor, Department of Chemistry, University of New Orleans, LA
07/2012 – present	Adjunct Professor, Department of Chemistry, University of New Orleans, LA
07/2012 – 06/2014	Assistant Professor, Department of Pharmaceutical Sciences, Univ. of California, Irvine
12/2012 – 06/2014	Assistant Professor (joint), Department of Chemistry, Univ. of California, Irvine
07/2014 – present	Associate Professor, Department of Pharmaceutical Sciences, Univ. of California, Irvine
07/2014 – present	Associate Professor (joint), Department of Chemistry, Univ. of California, Irvine
06/2013 – present	Scientific Advisory Board, Schrödinger Software, New York, NY

Honors and Awards
2014	National Science Foundation CAREER Award
2009	Hewlett Packard Outstanding Junior Faculty Award, American Chemical Society
2003	Graduate Fellowship, Kavli Institute for Theoretical Physics, UC Santa Barbara
2001-2003	National Science Foundation NEAT-IGERT Fellowship, UC Davis
2000-2001	UC Davis Physics Department Award
2000	Saxon-Patten Prize, UC Davis
2000	Departmental Citation in Physics, Physics Department, UC Davis
2000	Howard Hughes Medical Institute Science Teaching Internship

Other Experience and Professional Memberships
American Chemical Society
Biophysical Society

C. CONTRIBUTIONS TO SCIENCE

To date, I have published more than 50 articles in peer-reviewed journals, which have collectively received over 3800 citations in the literature. My current h-index is 30, and my i10-index is 43.

1. **Predictive absolute binding free energy calculations:** Alchemical binding free energy calculations initially showed considerable promise for helping to guide early stage pharmaceutical drug discovery by predicting protein-ligand interactions in advance of the synthesis of new ligands. However, by the time I began my postdoctoral work early enthusiasm had waned and applications of these techniques were relatively rare, largely because of challenges relating to automation (addressed more below) and technical and conceptual

issues relating to the calculation of absolute binding free energies. However, publications in 1997 and 2003 removed the major challenges hampering application of absolute techniques and paved the way for new success with free energy calculations. My work in this area was the first to apply absolute binding free energy calculations prospectively, to make (experimentally verified) blind predictions in a series of three different binding sites. We also demonstrated the thermodynamic importance of key aspects of binding such as ligand orientational sampling and protein conformational changes. This work made absolute binding calculations practical for the first time, and helped spark a resurgence of interest in these techniques. My role in this work was to design, oversee, and in some cases conduct the research (the work began when I was a postdoc, and I actually conducted it, but then as I started my own group I oversaw the work of students on these projects).

a. D. L. Mobley, A. P. Graves, J. D. Chodera, A. C. McReynolds, B. K. Shoichet and K. A. Dill, "Predicting absolute ligand binding free energies to a simple model site," *J. Mol. Biol.* **371**(4): 1118-1134 (2007).

b. S. E. Boyce, D. L. Mobley, G. Rocklin, A. P. Graves, K. A. Dill, B. K. Shoichet. "Predicting ligand binding affinity with alchemical free energy methods in a polar model binding site", *J. Mol. Biol.* **394:** 747-763 (2009).

c. G. J. Rocklin, S. E. Boyce, M. Fisher, I. Fish, D. L. Mobley, B. K. Shoichet*, and K. A. Dill*. "Blind prediction of charged ligand binding affinities in a model binding site", *J. Mol. Biol.* **425**(22):4569-4583 (2013).

2. **Automation of relative free energy calculations**. Relative free energy techniques were more established than absolute calculations, but applications were small in scale and limited due to the difficulty of setting up and conducting these calculations. We developed an automated approach for planning and setting up relative free energy calculations, and also improved automation of analysis. This allowed these calculations to be applied on a large scale, including in drug discovery applications, for the first time. I planned and oversaw the work on automated planning, with collaborators inside and outside my group, and then collaborated with colleagues in industry who implemented the approach in their software for industrial applications.

a. S. Liu, Y. Wu, T. Lin, R. Abel, J. Redmann, C. M. Summa, V. R. Jaber, N. M. Lim, and D. L. Mobley, "Lead Optimization Mapper: Automating free energy calculations for lead optimization", *J. Comput. Aided Mol. Design* **27**(9):755-770 (2013).

b. L. Wang, Y. Wu, Y. Deng, B. Kim, L. Pierce, G. Krilov, D. Lupyan, S. Robinson, M. K. Dahlgren, J. Greenwood, D. L. Romero, C. Masse, J. L. Knight, T. Steinbrecher, T. Beuming, W. Damm, E. Harder, W. Sherman, M. Brewer, R. Wester, M. Murcko, L. Frye, R. Farid, T. Lin, D. L. Mobley, W. L. Jorgensen, B. J. Berne, R. A. Friesner, and R. Abel. "Accurate and reliable prediction of relative ligand binding potency in prospective drug discovery by way of a modern free-energy calculation protocol and force field", *J. Am. Chem. Soc.* 137(7):2695-2703 (2015).

c. P. V. Klimovich, M. R. Shirts and D. L. Mobley, "Guidelines for the analysis of free energy calculations", *J. Comput. Aided Mol. Design.* **29**(5):397-411 (2015).

3. **Testing force fields using solvation free energies**. The accuracy of computed binding free energies depends crucially on the accuracy of the underlying force fields. We realized this and began using solvation free energies as a way to test and identify systematic errors in our force fields, with benefits for binding free energy calculations. We also used our work comparing to experiment in this area to develop a database of calculated and experimental hydration free energies that is widely used in a variety of contexts to help test and improve models. I planned, oversaw, and in some cases conducted this work, which took place in my group (after the initial study, which I did as a postdoc) with help from outside collaborators.

a. D. L. Mobley, C. I. Bayly, M. D. Cooper, M. R. Shirts, and K. A. Dill. "Small molecule hydration free energies in explicit solvent: An extensive test of fixed-charge force fields", *J. Chem. Theory Comput.* **5:** 350-358 (2009).

b. P. V. Klimovich and D. L. Mobley, "Predicting hydration free energies using all-atom molecular dynamics simulations and multiple starting conformations", J. Computer-Aided Molecular Design **24**: 307-316 (2010).

c. D. L. Mobley**,** S. Liu, D. Cerutti, W. C. Swope, and J. Rice, "Alchemical prediction of hydration free energies for SAMPL", special issue, *J. Comput. Aided Mol. Design* **26**(5):551-562 (2012).

d. C. J. Fennell, K. L. Wymer, and D. L. Mobley, "A fixed-charge model for alcohol polarization in the condensed phase, and its role in small molecule hydration", *J. Phys. Chem. B* **118**(24):6438-6446 (2014). Invited article.

e. D. L. Mobley and J. P. Guthrie, "FreeSolv: A database of experimental and calculated hydration free energies, with input files," *J. Comput. Aided Mol. Design* **28**:711-720 (2014).

4. **Participating in and organizing blind SAMPL challenges**: As noted above, SAMPL blind predictive challenges have played a key role in our work since our first entrance into blind challenges in #1 above. In 2014, I actually transitioned to running the SAMPL challenge, soliciting predictions of a variety of properties from the computational community all over the world. This challenge provides, and will continue to provide, a valuable opportunity for testing and comparing different methods. In addition to the work noted under A, the following important publications have resulted from our work in SAMPL:

    a. C. C. Bannan, K. H. Burley, M. Chiu, M. R. Shirts, M. K. Gilson, and D. L. Mobley, "Blind prediction of cyclohexane-water distribution coefficients from the SAMPL5 challenge", *J. Comput. Aided Mol. Design*, in press.

    b. T. S. Peat, O. Dolezal, J. Newman, D. L. Mobley, J. J. Deadman, "Interrogating HIV integrase for compounds that bind – a SAMPL4 challenge", *J. Comput. Aided Mol. Design* 28:347-362 (2014).

    c. **D. L. Mobley,** S. Liu, D. Cerutti, W. C. Swope, and J. Rice, "Alchemical prediction of hydration free energies for SAMPL", special issue, *J. Comput. Aided Mol. Design* **26**(5):551-562 (2012).

    d. P. V. Klimovich and **D. L. Mobley**, "Predicting hydration free energies using all-atom molecular dynamics simulations and multiple starting conformations", J. Computer-Aided Molecular Design **24**: 307-316 (2010).

Full list of published work available at MyNCBI:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/43376427/?sort=date&direction=ascending

D. RESEARCH SUPPORT
Ongoing Research Support

1R01GM108889-01 (NIH)   Mobley (PI)   9/1/2014-8/31/2019
Alchemical free energy methods for efficient drug lead optimization
This study focuses on automating planning of protein simulation-based relative free energy calculations for drug lead discovery, on improving methods for sampling ligand and protein motions in molecular simulations, and on applying these techniques to several drug discovery projects.
Role: PI

CHE-1352608 (NSF)   Mobley (PI)   07/15/2014-07/14/2019
CAREER: Computing accurate free energies for solubility, solvation and transfer
This study focuses on developing and applying molecular-simulation-based techniques for prediction of solvation free energies, transfer free energies and transfer properties, and solubilities.
Role: PI

Completed Research Support

1R15GM096257-01A1 (NIH)   Mobley (PI)   3/1/2012-2/28/2015
(At the University of New Orleans)
Improving alchemical methods for predicting protein-ligand binding
The goal of this study is to test alchemical binding free energy techniques on three different binding sites, incorporating sampling enhancements relating to binding mode and sidechain sampling as needed.
Role: PI

1450865 (NSF)   Mobley (PI)   02/15/2015-01/31/2016
Accelerating our Understanding of Supramolecular Chemistry in Aqueous Solutions: A Workshop Proposal

This provided funds for a workshop in Arlington, VA in June, 2015 bringing together physical and supramolecular chemists to plan how to move the field forward and facilitate knowledge transfer between the physical and supramolecular chemistry communities.
Role: co-PI