OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.  
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NAME: Lee, Tai-Sung

eRA COMMONS USER NAME (credential, e.g., agency login): Taisung

POSITION TITLE: Associate Research Professor

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 |
| --- | --- | --- | --- |
| National Taiwan University, Taipei | BS | 05/1988 | Chemistry |
| National Taiwan University, Taipei | MS | 05/1990 | Physical Chemistry |
| Duke University, Durham, North Carolina | PHD | 02/1997 | Theoretical Chemistry |
| University of California, San Francisco, San Francisco, California | Postdoctoral Fellow | 09/2000 | NIH Postdoc in Biosimulation |
| American College of Medical Genetics | Other training | 04/2006 | Accumulated 23.5 Continue Medical Education |

### A. PERSONAL STATEMENT

My roles in the proposed project is to utilize GPU-accelerated free energy calculations to evaluate the to-be-developed force fields. Apparently, it requires expertise in two areas: a.) free energy methods/simulations; b.) GPU-accelerated simulations:

**In the field of free energy methods/molecular simulations:**

Trained as a theoretical chemist, I developed the first linear-scaling quantum calculations on biological systems using the “divide-and-conquer” method. At UCSF, during my postdoc work, my background was extended broadly to biological simulations using quantum, molecular dynamics, and QM/MM methods, as well as in-depth experience in free energy methods, which is clearly shown in my 68 peer-reviewed journal articles.

**In the field of software engineering/GPU-accelerated methods:**

On the software engineer side: I had formal training in computer science (24 credits in college) and over 20 years of programming experience. From 2000 to 2005, I worked as a scientific programmer and then a software project manager in an industrial setting, which gave me precious experience not only in rigorous object-oriented software design and development but also in large-scale software management.

From 2016, I have devoted into GPU-accelerated free energy implementation in Amber16/18 and am the main author of both the code and resulting papers.

Specifically for the proposed work. I am active in free energy methodology/implementation and in protein-ligand binding system simulations.

1. Lee TS, Cerutti DS, Mermelstein D, Lin C, LeGrand S, Giese TJ, Roitberg A, Case DA, Walker RC, York DM. GPU-Accelerated Molecular Dynamics and Free Energy Methods in Amber18: Performance Enhancements and New Features J Chem Inf Model. 2018 Oct 22;58(10):2043-2050 PubMed PMID: 30199633.
2. Lee TS, Hu Y, Sherborne B, Guo Z, York DM. Toward Fast and Accurate Binding Affinity Prediction with pmemdGTI: An Efficient Implementation of GPU-Accelerated Thermodynamic Integration. J Chem Theory Comput. 2017 July 11;13(7):3077-3084. PubMed PMID: 28618232.
3. Lee TS, Radak BK, Huang M, Wong KY, York DM. Roadmaps through free energy landscapes calculated using the multi-dimensional vFEP approach. J Chem Theory Comput. 2014 Jan 14;10(1):24-34. PubMed PMID: 24505217; PubMed Central PMCID: PMC3912246.
4. Lee TS, Kollman PA. Free energy calculation in rational drug design. Reddy MR, Erion MD, editors. New York: Kluwe Academic/Plenum Publishers; 2001. Chapter 17, Thymidylate synthase: free energy calculations for estimating inhibitor binding affinities; p.335-342.

### B. POSITIONS AND HONORS

Positions and Employment

|  |  |
| --- | --- |
| 1998 - 2000 | NIH Postdoctoral fellow, University of California, San Francisco , San Francisco , CA |
| 2000 - 2002 | Staff Scientist, Accelrys, Inc., San Diego, CA |
| 2002 - 2002 | Senior Scientist, Accelrys, Inc., San Diego, CA |
| 2002 - 2005 | Project Lead, Accelrys, Inc., San Diego, CA |
| 2005 - 2010 | Bioinformatics Consultant, Nichols Research Institute, Quest Diagnostics, San Juan Capistrano, CA |
| 2006 - 2008 | Visiting Scholar, Consortium for Bioinformatics & Computational Biology, University of Minnesota, Minneapolis, MN |
| 2006 - 2010 | Senior Scientist, Department of Chemistry, University of Minnesota, Minneapolis, MN |
| 2010 - 2015  2015 - 2016  2016 - | Associate Research Professor, BioMaPS Institute and Department of Chemistry, Rutgers, The State University of New Jersey, Piscataway, NJ  Associate Research Professor, Center for Integrative Proteomics Research, Rutgers, The State University of New Jersey, Piscataway, NJ  Associate Research Professor, Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, NJ |

Other Experience and Professional Memberships

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| --- | --- |
| 1992 - | Member, American Chemical Society |

Honors

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| --- | --- |
| 1990 | Graduated w/ First Place Honor, National Taiwan University |
| 1993 | Cray Research Fellowship, Cray Research Inc. |
| 1994 | William R. Krigbaum Fellowship, Duke University |
| 1996 | P. M. Gross Fellowship, Duke University |
| 1998 | NIH F32 Postdoctoral Fellow, NIH |
| 2002 | Accelrys Circle of Excellence Award (Top 1% employee), Accelrys, Inc. |

### C. Contribution to Science

1. **The first full-quantum description of protein systems with 10,000 atoms:** Developed the “divide-and-conquer” approach for quantum chemical calculations. The approach has been successfully applied to various important problems, including electronic structure calculations, solvent effect studies, enzymatic reactions and pKa calculations for biomolecules.
   1. Yang W, Lee TS. A density-matrix divide-and-conquer approach for electronic structure calculations of large molecules. J Chem Phys. 1995; 103:5674-5678.
   2. Lee TS, York DM, Yang W. Linear-scaling semiempirical quantum calculations for macromolecules. J Chem Phys. 1996; 105:2744-2750.
   3. Lee TS, Lewis JP, Yang W. Linear-scaling quantum mechanical calculations of biological molecules: the divide-and-conquer approach. Comp Mater Sci. 1998; 12:259--277.
   4. York DM, Lee TS, Yang W. Quantum mechanical treatment of biological macromolecules in solution using linear-scaling electronic structure methods. Phys Rev Lett. 1998; 80:5011-5014.
2. **Drug design based on free energy estimations:** Theoretical study of enzyme-inhibitor interactions by free energy perturbation and molecular dynamics methods and free energy calculations and molecular dynamics studies on site-specific mutagenesis.
   1. Lee TS, Kollman PA. Theoretical studies suggest a new antifolate as a more potent inhibitor of thymidylate synthase. J Am Chem Soc. 2000; 122:4385-4393.
   2. Lee TS, Massova I, Kuhn B, Kollman PA. QM and QM-FE simulations on reactions of relevance to enzyme catalysis: trypsin, COMT, beta-lactamase and pseudouridine synthetase. J Chem Soc Perkin Trans 2. 2000; 3:409-415.
   3. Kollman PA, Massova I, Reyes C, Kuhn B, Huo S, et al. Calculating structures and free energies of complex molecules: combining molecular mechanics and continuum models. Acc Chem Res. 2000 Dec;33(12):889-97. PubMed PMID: [11123888](http://www.ncbi.nlm.nih.gov/pubmed/11123888/).
   4. Lee TS, Kollman PA. Free energy calculation in rational drug design. Reddy MR, Erion MD, editors. New York: Kluwe Academic/Plenum Publishers; 2001. Chapter 17, Thymidylate synthase: free energy calculations for estimating inhibitor binding affinities; p.335-342.
3. **A confirmed prediction of an overlooked alternative splicing of BCR-ABL1:** The imatinib resistance due to an overlooked alternative splicing mutant, 35INS, was predicted through simulations. This prediction was later confirmed in vivo and in vitro. Related work includes drug resistance analysis for other BCR-ABL1 mutants.
   1. Lee TS, Potts SJ, Kantarjian H, Cortes J, Giles F, et al. Molecular basis explanation for imatinib resistance of BCR-ABL due to T315I and P-loop mutations from molecular dynamics simulations. Cancer. 2008 Apr 15;112(8):1744-53. PubMed PMID: [18338744](http://www.ncbi.nlm.nih.gov/pubmed/18338744/).
   2. Lee TS, Ma W, Zhang X, Giles F, Cortes J, et al. BCR-ABL alternative splicing as a common mechanism for imatinib resistance: evidence from molecular dynamics simulations. Mol Cancer Ther. 2008 Dec;7(12):3834-41. PubMed PMID: [19056677](http://www.ncbi.nlm.nih.gov/pubmed/19056677/).
   3. Lee TS, Ma W, Zhang X, Albitar M, Giles F, et al. BCR-ABL1INS35 Is Not Uncommon in CML Patients and Is Related to Resistance and Sensitivity to Inhibitors in CML Treatment. Mol Cancer Ther. 2010; 9:772-772.
   4. Lee TS, Potts SJ, Albitar M. Molecular Dynamic Studies Unveil Potential Mechanisms of Resistance to Imatinib in BCR-ABL Mutants. Topics in Anti-Cancer Research. 2014; 3:319-341.
4. **The first atomic level explanation of JAK2 auto-regulation and V617F constitutive activation mechanism:** Significant findings of JAK2 auto-regulation mechanism and the constitutive activation due to V617F were revealed through simulations, as well as simulations on various clinically observed mutants.
   1. Lee TS, Ma W, Zhang X, Giles F, Kantarjian H, et al. Mechanisms of constitutive activation of Janus kinase 2-V617F revealed at the atomic level through molecular dynamics simulations. Cancer. 2009 Apr 15;115(8):1692-700. PubMed PMID: [19195039](http://www.ncbi.nlm.nih.gov/pubmed/19195039/).
   2. Lee TS, Ma W, Zhang X, Kantarjian H, Albitar M. Structural effects of clinically observed mutations in JAK2 exons 13-15: comparison with V617F and exon 12 mutations. BMC Struct Biol. 2009 Sep 10;9:58. PubMed PMID: [19744331](http://www.ncbi.nlm.nih.gov/pubmed/19744331/); PubMed Central PMCID: [PMC2749040](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2749040/).
   3. Lee TS. On the regulation and activation of JAK2: a novel hypothetical model. Mol Cancer Res. 2013 Aug;11(8):811-4. PubMed PMID: [23615525](http://www.ncbi.nlm.nih.gov/pubmed/23615525/).
5. **The first successful atomic-level detailed predictions of the Mg2+ ion roles in the Hammerhead Ribozyme reaction** and explanations/predictions of the mutational effects of 14 observed and predicted mutants.
   1. Lee TS, López CS, Martick M, Scott WG, York DM. Insight into the role of Mg in hammerhead ribozyme catalysis from X-ray crystallography and molecular dynamics simulation. J Chem Theory Comput. 2007 Mar;3(2):325-327. PubMed PMID: [19079784](http://www.ncbi.nlm.nih.gov/pubmed/19079784/); PubMed Central PMCID: [PMC2600717](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2600717/).
   2. Lee TS, Silva López C, Giambasu GM, Martick M, Scott WG, et al. Role of Mg2+ in hammerhead ribozyme catalysis from molecular simulation. J Am Chem Soc. 2008 Mar 12;130(10):3053-64. PubMed PMID: [18271579](http://www.ncbi.nlm.nih.gov/pubmed/18271579/); PubMed Central PMCID: [PMC2535817](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2535817/).
   3. Lee TS, Potts SJ, Kantarjian H, Cortes J, Giles F, et al. Molecular basis explanation for imatinib resistance of BCR-ABL due to T315I and P-loop mutations from molecular dynamics simulations. Cancer. 2008 Apr 15;112(8):1744-53. PubMed PMID: [18338744](http://www.ncbi.nlm.nih.gov/pubmed/18338744/).
   4. Lee TS, Giambaşu GM, Sosa CP, Martick M, Scott WG, et al. Threshold occupancy and specific cation binding modes in the hammerhead ribozyme active site are required for active conformation. J Mol Biol. 2009 Apr 24;388(1):195-206. PubMed PMID: [19265710](http://www.ncbi.nlm.nih.gov/pubmed/19265710/); PubMed Central PMCID: [PMC2715853](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2715853/).

PubMed publication: <http://www.ncbi.nlm.nih.gov/sites/myncbi/tai-sung.lee.1/bibliography/47551178/public/?sort=date&direction=descending>

**D. Additional Information: Research Support and/or Scholastic Performance**

Ongoing and Completed Research Support

1. National Institutes of Health (Grant R01GM107485)

*Next-generation integrated quantum force fields for biomedical applications*

08/01/2015-03/31/2019 (PI: Darrin York)

Role: Staff Scientist

Methodology driven grant to create new quantum mechanical force fields to study biomolecular systems.

1. National Institutes of Health (Grant R01GM62248)

*Computational enzymology to study diverse catalytic strategies of RNA.*

08/01/2014-08/31/2022 **(**PI: Darrin York)

Role: Faculty

Current grant: Application driven grant to study mechanisms of ribozyme catalysis using novel multiscale quantum models and molecular simulation tools.