BIOGRAPHICAL SKETCH

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NAME: **John D. Chodera**

eRA COMMONS USER NAME: **JCHODERA**

POSITION TITLE: **Associate Member,** Computational and Systems Biology Program

EDUCATION/TRAINING

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| --- | --- | --- | --- |
| INSTITUTION AND LOCATION | DEGREE | Completion Date | FIELD OF STUDY |
| California Institute of Technology | BS | 06/1999 | Biology |
| University of California, San Francisco | PhD | 12/2006 | Biophysics |
| Stanford University | Postdoc | 2007-2008 | Chemistry |
| QB3 Fellow, University of California, Berkeley | Postdoc | 2008-2012 | Quantitative Biosciences |

**A. Personal Statement**

My research focuses on the development and application of predictive, quantitative computational chemistry models and algorithms for drug discovery that integrate physical modeling with machine learning to prioritize the synthesis of potent, selective small molecules and predict the emergence of drug resistance via mutational mechanisms. My laboratory consists of theorists and experimentalists that combine statistical mechanical theory, machine learning, biomolecular simulation, and biophysical measurements to accelerate drug discovery. I have extensive experience in the development and application of alchemical free energy calculations for the prediction of small molecule binding affinities and selectivities to protein targets---a technique now used extensively in structure-enabled drug discovery thanks to our work in this area. I am a founding member of the Folding@Home Consortium---the largest distributed computing platform for biomolecular simulation which recently became the world’s first exascale computing resource. I am actively involved in developing new approaches and open source tools that combine AI and high-throughput experimentation to accelerate and automate design-make-test-analyze cycles to accelerate, improve success rates, and reduce costs of drug discovery. My experimental laboratory is entirely automated, featuring liquid-handling robotics, automating plate handling, and multiple integrated detection modalities.

**B. Positions and Honors**

**Positions and Employment (***current positions in* ***bold)***

2005 IBM Almaden Research summer internship, Blue Gene project, under William C. Swope

2007-2008 Postdoctoral Fellow, Department of Chemistry, Stanford University

2008-2012 QB3 Distinguished Postdoctoral Fellow, University of California, Berkeley, Berkeley, CA

2012-2019 **Assistant Member** and Laboratory Head, Computational Biology Program,

Sloan Kettering Institute for Cancer Research, MSKCC

2013-present **Faculty Member**, Program in Physiology, Biophysics, and Systems Biology,

Weill Cornell Graduate School of Medical Sciences

2013-present **Faculty Member**, Tri-Institutional PhD Program in Chemical Biology

2013-present **Faculty Member**, Tri-Institutional PhD Program in Computational Biology and Medicine

2015-present **Faculty Member**, Gerstner Sloan Kettering Graduate School of Medical Sciences, MSKCC

2019-present **BIH Einstein Visiting Fellow**, Charité Universitätmedezin Berlin

2019-present **Associate Member** and Laboratory Head, Computational Biology Program,

Sloan Kettering Institute for Cancer Research, MSKCC (primary appointment)

**Honors and Awards**

2000-2005 Howard Hughes Medical Institute Predoctoral Fellowship

2005-2006 IBM Predoctoral Fellowship

2008-2012 QB3-Berkeley Distinguished Postdoctoral Fellowship

2013-2016 Louis V. Gerstner Young Investigator Award

2017 Silicon Therapeutics Open Science Fellowship

2020-2022 BIH Einstein Visiting Fellowship, Charité Universitätmedezin Berlin

**Other Experience and Professional Memberships**

2000-present Member, American Chemical Society

2014-2018 Scientific Advisory Board, Schrödinger

2018-present Scientific Advisory Board, OpenEye

2020-present Scientific Advisory Board, Redesign Science

2021-present Scientific Advisory Board, Interline Therapeutics

**C. Contributions to Science**

As of 2 Sep 2021, I have published more than 85 articles in peer-reviewed journals, which have collectively received over 13,955 citations in the literature. My current h-index is 50, and my i10-index is 93.

**1.** **Accurate alchemical free energy calculations for small molecule drug discovery.** With the aim of enabling true *computer-driven* *design* of small molecules as potential therapeutics and chemical probes, I have spent over a decade developing alchemical free energy methodologies into a quantitative, predictive tool for accurate computation of small molecule binding affinities to biomolecular targets. Work I have led or contributed to has benchmarked and improved the accuracies of free energy calculations, fixed deficiencies in methodologies, helped establish best practices, developed new efficient simulation algorithms, and exploited high-performance graphics computing hardware (GPUs) to greatly advance our progress toward this goal. Our open source tools are now used by multiple industrial partners. New preprints and papers in this area demonstrate (a) our development of a new generation of alchemical free energy calculations that can systematically improve accuracy on experimental data collected for similar compounds, (b) our use of new machine learning potentials to achieve ultra-high accuracy in protein-ligand affinities, (c) demonstration that alchemical free energy calculations can accurately predict selectivity or affinity to related targets, and (d) codification of the best practices for achieving high accuracy with these methods.

1. Wieder M, Fass J, and **Chodera JD.** Teaching free energy calculations to learn from experimental data. BioRxiv **[Preprint]** August 26, 2021. Available from: <https://doi.org/10.1101/2021.08.24.457513>
2. Rufa DA, Bruce Macdonald HE, Fass J, Wieder M, Grinaway PB, Roitberg AE, Isayev O, and **Chodera JD**. BioRxiv **[Preprint]** July 30, 2020. Available from: <https://doi.org/10.1101/2020.07.29.227959>
3. Albanese SK, **Chodera JD,** Volkamer A, Keng S, Abel R, and Wang L. Is structure based drug design ready for selecftivity optimization? *Journal of Chemical Informatics and Modeling* 60:12, 2020. PMCID: PMC8310368
4. Mey SJS, Allen B, Bruce Macdonald HE, **Chodera JD,** Kuhn M, Michel J, Mobley DL, Naden LN, Prasad S, Rizzi A, Scheen J, Shirts MR, Tresadern G, and Xu H. *Living Journal of Computational Molecular Sciences* 2022. <https://doi.org/10.33011/livecoms.2.1.18378>

3. **Prediction of drug resistance via point mutations.** We have been developing alchemical free energy calculations as a means of predicting the emergence of resistance via point mutations. This is illustrated by our work in (a) predicting the impact of point mutations on kinase inhibitor affinity, (b) new experimental approaches to measure the impact of point mutations on inhibitor binding, (c) assessment of the impact of point mutations in SARS-CoV-2.

1. Hauser K, Negron C, Albanese S, Ray S, Steinbrecher T, Abel R, **Chodera JD**, and Wang L. (2018) Communications Biology 1:70. Predicting resistance of clinical Abl mutations to targeted kinase inhibitors using alchemical free-energy calculations. PMCID: PMC6110136
2. Lyczek A, et al., Knapp S, **Chodera JD,** and Seeliger MA. BioRxiv **[Preprint]** June 28, 2021. Available from: <https://doi.org/10.1101/2021.06.28.449968>
3. Starr T, et al., **Chodera JD,** Hebner CM, Whelan SPJ, Virgin HW, Veesler D, Corti D, Bloom JD, and Snell G. *Nature* 597:97, 2021.

**3. Drug discovery.** I have spent the past decade working on quantitative predictive tools to accelerate drug discovery. This work is illustrated by collaboratons such as (a) the COVID Moonshot, which has made rapid progress toward patent-free small molecule inhibitors of SARS-CoV-2 Mpro; (b) the identification and characterization of a pan-Id agonist, (c) the identification and characterization of an inhibitor of the RNA-binding protein MUSASHI, and (d) identifying the mechanism of therapeutic resistance to IDH inhibitors.

1. **Chodera JD**, Lee AA, London N, and von Delft F. Crowdsourcing drug discovery for pandemics. *Nature Chemistry* 12:581, 2020.
2. Wojnarowicz PM, et al., **Chodera JD,** Pavletich N, Lasorella A, Campochiaro PA, and Benezra R. A small molecule pan-Id agonist inhibits pathologic ocular neovascularization. *Cell Reports* 29:62, 2019. PMCID: PMC6896334
3. Minuesa G, et al., **Chodera JD,** and Kharas MG. Small-molecule targeting of MUSASHI RNA-binding activity in acute myeloid leukemia. *Nature Communications* 10:2691, 2019. PMCID: PMC6584500
4. Intelkofer AM, et al., **Chodera JD,** Thompson CB, Levin RL, and Stein EM. Acquired resistance to IDH inhibition through trans or cis dimer-interface mutations. *Nature* 559:125, 2018. PMCID: PMC6121718

**4. Biomolecular conformational dynamics and structural biology.** Biological macromolecules are not static entities, but populate a variety of kinetically metastable conformational states critical to binding and function. The long lifetimes of these metastable states present a challenge for molecular simulation, which are generally limited in length to a few microseconds. Together with collaborators at Stanford, the IBM Almaden Research Center, and the Freie Universität Berlin, I developed an approach to use *Markov state models* (MSMs) to build stochastic models of the long-time dynamics of biomolecules from many short atomistically-detailed molecular simulations. This technique allows for the characterization of thermally accessible metastable conformational states, along with their associated interconversion kinetics and equilibrium free energies, and is now utilized by many laboratories around the world. More recently, we have applied this technique to study protein reorganization free energies contributing to small molecule binding affinities and selectivities relevant to drug discovery.

1. Hanson SM, Georghiou G, Miller WT, Rest JS, **Chodera JD,** and Seeliger MA. What makes a kinase promiscuous for inhibitors? *Cell Chemical Biology* 26:390, 2019. PMCID: PMC6632086
2. Pitera, J.W. and **Chodera**, J.D. On the use of experimental observations to bias simulated observables. *Journal of Chemical Theory and Computation* 8:3445, 2012.
3. Noé F, Doose S, Daidone I, Löllmann M, Sauer M, **Chodera JD**, and Smith JC. Dynamical fingerprints: A theoretical framework for understanding biomolecular processes by combination of simulation and kinetic experiments. *Proceedings of the National Academy of Sciences USA* 108:4822, 2011. PMCID: PMC3064371
4. **Chodera JD**, Singhal N, Pande VS, Dill KA, and Swope WC. Automatic discovery of metastable states for the construction of Markov models of macromolecular conformational dynamics. *Journal of Chemical Physics* 126:155101, 2007. PMID: 174616665

**5.** **Advances in molecular simulation algorithms and methodologies.** Throughout my career, I have been active in the development of new algorithms to increase the efficiency of molecular simulations, establish best practices, benchmark and improve molecular mechanics forcefields, and exploit novel computing paradigms. Key advances include (a) a simple solution to the longstanding problem of detecting when a simulation has sufficiently equilibrated*,* (b) recognizing replica exchange simulations can be considered a form of Gibbs sampling, (c) new estimators for combing simulation data from a variety of temperatures, and (d) the development of a new GPU-accelerated molecular simulation framework*.*

1. **Chodera JD.** A simple method for automated equilibration detection in molecular simulations. *Journal of Chemical Theory and Computation* 12:1799, 2016. PMCID: PMC4945107
2. **Chodera JD** and Shirts MR. Replica exchange and expanded ensemble simulations as Gibbs sampling: Simple improvements for enhanced mixing. *Journal of Chemical Physics* 135:194110, 2011. PMID: 22112069
3. Prinz JH, **Chodera JD,** Pande VS, Swope WC, Smith JC, and Noé F. Optimal use of data in parallel tempering simulations for the construction of discrete-state Markov models of biomolecular dynamics. *Journal of Chemical Physics* 134:244108, 2011. PMCID: PMC3139503
4. Eastman P, Swails J, **Chodera, JD,** McGibbon RT, Zhao Y, Beauchamp KA., Wang LP, Simmonett, AC, Harrigan MP, Stern CD, Wiewiora RP, Brooks BR, and Pande VS. OpenMM 7: Rapid development of high performance algorithms for molecular dynamics. *PLoS Computational Biology* 13:e1005659, 2017. PMCID: PMC5549999

Complete list of published work available at MyNCBI Collections:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/john.chodera.1/bibliography/43349161/public>

**D. Research Support**

***Ongoing Research Support***

**Wellcome Trust Therapeutics Accelerator 224021/Z/21/Z** (PI: Perry) 7/1/2021 – 3/1/2023

Development of an investigational new drug from a novel, open-science, orally available small molecule anti-viral targeting SARS-CoV2 main protease

*The goal of this project is to field an accelerated preclinical development program to reach IND-equivalent approval for a first-generation non-covalent oral antiviral targeting SARS-CoV-2 Mpro discovered by the COVID Moonshot.*

**NIH 1R01GM121505-01** (PI: Chodera) 9/15/2017 – 8/31/2017

The role of reorganization energy in achieving selective kinase inhibition

*The goal of this project is to characterize the role of conformational reorganization energetics in achieving targeted kinase inhibitor selectivity and model the impact of point mutations on resistance.*

**Relay Biotherapeutics // SK2018-0162** (PI: Chodera) 7/25/2019 – 7/24/2021

Development of efficient open source cloud-enabled free energy based lead optimization algorithms and integrative Bayesian model of experimental biophysical and molecular simulation data

*The goal of this project is to develop open source scalable cloud workflows for lead optimization using relative and absolute alchemical free energy calculations.*

**Vir Biotherapeutics // SK2019-0582** (PI: Chodera) 7/25/2019 – 7/24/2021

Developing physical models of antibody:antigen affinity

*The objective of this project is to develop new physical modeling methods based on alchemical free energy calculations to predict the impact of point mutations on SARS-CoV-2 therapeutic efficacy*

**NIH 1R01GM121270-01A1** (Co-I; PI: Mobley, UCI) 9/10/2018 – 8/31/2022

Advancing predictive physical modeling through focused development of model systems to drive new modeling innovations

*The goal of this project is to achieve quantitative accuracy in the field of computational physical modeling of drug-receptor interactions via blind community challenges*

***Completed Research Support***

**NSF CHE-2033426** (PI: Chodera) 7/1/2020 – 6/30/2021

RAPID: Identifying biophysical determinants of binding to the SARS-CoV-2 main viral protease

*The goal of this project is to use the Folding@home exascale distributed computing platform to conduct large-scale binding free energy calculations to prioritize the synthesis of new compounds that maximize SARS-CoV-2 main viral protease binding and inhibition.*