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Education and positions

- 2019–2021 BIH Einstein Visiting Professor, Charité, Berlin
- 2018– Associate Member, Memorial Sloan-Kettering Cancer Center
- 2018– Associate Professor, Physiology, Biophysics, and Systems Biology Program,
Weill Cornell Graduate School of Medical Sciences
- 2013–2018 Assistant Professor, Physiology, Biophysics, and Systems Biology Program,
Weill Cornell Graduate School of Medical Sciences
- 2012–2018 Assistant Member, Memorial Sloan-Kettering Cancer Center
- 2008–2012 Independent Distinguished Postdoctoral Fellow, California Institute for Quantitative Biosciences (QB3),
University of California, Berkeley
- Independent research funding, sponsors [Phillip L. Geissler](#) and [Susan Marqsee](#)
- 2007–2008 Postdoctoral researcher, Department of Chemistry, Stanford University
With [Vijay S. Pande](#) (head of [Folding@Home](#) distributed computing project)
- 1999–2006 Ph.D. in Biophysics, University of California, San Francisco
Committee: [Ken A. Dill](#), [Matthew P. Jacobson](#), [Vijay S. Pande](#)
- 1995–1999 B.S. in Biology, California Institute of Technology
Undergraduate research with [Paul H. Patterson](#) (*molecular neurobiology*) and Jerry E. Solomon (*computational chemistry*)

Fellowships and awards

- 2019–2021 BIH Einstein Visiting Fellowship
- 2017 Silicon Therapeutics Open Science Fellowship
- 2013–2016 Louis V. Gerstner Young Investigator Award
- 2013–2014 Google Exacycle for External Faculty
- 2008–2012 QB3-Berkeley Distinguished Postdoctoral Fellowship, University of California, Berkeley
- 2005–2006 IBM Predoctoral Fellowship
- 2000–2005 Howard Hughes Medical Institute Predoctoral Fellowship

Research overview

My research focuses on **bringing physical modeling into the high-throughput biology and genomics era and reimagining the way we develop small molecules for chemical biology and drug discovery**. By combining novel algorithmic advances to achieve orders-of-magnitude efficiency gains with powerful but inexpensive GPU hardware, machine learning, and distributed computing technologies, my lab is developing next-generation approaches and open source software for predicting small molecule binding affinities, designing small molecules with desired properties, predicting the drug sensitivity or resistance of clinical mutations, and understanding the detailed structural mechanisms underlying oncogenic mutations. We co-develop the [OpenMM](#) GPU-powered molecular simulation framework, which powers numerous biomolecular modeling and simulation applications using physical modeling and machine learning. As a core member of the [Folding@home Consortium](#), my lab harnesses the largest computing platform in the world—the first to reach an exaFLOP/s—pooling the efforts of a million volunteers around the world to study functional implications of mutations and new opportunities for therapeutic design against cancer targets and global pandemics. I co-founded the [Open Force Field Initiative](#), a scientific collaboration funded by the NIH and an industry consortium consisting of dozens of scientists working to develop modern open source infrastructure for building and applying high-quality biomolecular force fields. I am a founding member of the <http://postera.ai/covid>, a radical open science patent-free drug discovery effort aiming to develop an inexpensive small molecule therapy effective against COVID-19 and future coronavirus. Using automated biophysical measurements, my laboratory collects new experimental data targeted to advance the quantitative accuracy of our methodologies, and gather new insight into drug susceptibility and resistance in kinases and other cancer targets. My work makes extensive use of scalable Bayesian statistical inference, machine learning via probabilistic programming, and information theoretic principles for designing experiments and quantifying error. I am passionate about open science, disseminating scientific best practices, and maximizing research reproducibility.

Software

Major codes developed by our lab can be found at <http://choderalab.org/code>

All software is licensed under permissive OSI-approved open source licenses and available on [GitHub](#)

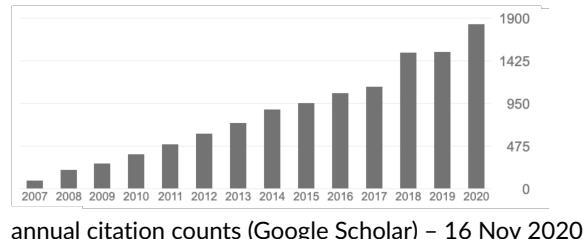
Publications

All publications: <http://choderalab.org/publications>
Google Scholar statistics: <http://goo.gl/qO0JW>
MyNCBI Bibliography: <http://goo.gl/e3kjgK>
bioRxiv preprints: <https://bit.ly/2LHGwxJ>
arXiv preprints: <https://bit.ly/2Rp2Y3T>
chemRxiv preprints: <https://chemrxiv.org/search?q=chodera>
Open source software: <http://choderalab.org/code>
Major datasets: <http://choderalab.org/data>
h-index: 47 / i10-index: 79 / citations: 11776 (16 Nov 2020)

* denotes co-first-authors

† denotes co-second-authors

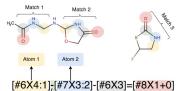
‡ denotes co-corresponding authors



annual citation counts (Google Scholar) – 16 Nov 2020

Preprints

Preprint · chemRxiv



Qiu Y, Smith DGA, Boothroyd B, Jang H, Wagner J, Bannan C, Gokey T, Lim VT, Stern CD, Rizzi A, Lucas X, Tjanaka B, Shirts MR[‡], Gilson MK[‡], Chodera JD[‡], Bayly CI[‡], Mobley DL[‡], Wang L-P[‡]

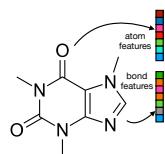
Development and benchmarking of Open Force Field v1.0.0, the Parsley small molecule force field

We present a new, modern small molecule force field for molecular design from the Open Force Field Initiative, a large industry-academic collaboration that focuses on open science, open data, and modern open source infrastructure.

Preprint · arXiv

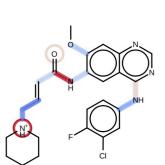
Wang Y, Fass J, and Chodera JD

End-to-end differentiable molecular mechanics force field construction



Molecular mechanics force fields have been a workhorse for computational chemistry and drug discovery. Here, we propose a new approach to force field parameterization in which graph convolutional networks are used to perceive chemical environments and assign molecular mechanics (MM) force field parameters. The entire process of chemical perception and parameter assignment is differentiable end-to-end with respect to model parameters, allowing new force fields to be easily constructed from MM or QM force fields, extended, and applied to arbitrary biomolecules.

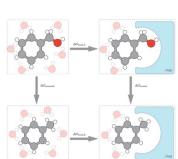
Preprint · bioRxiv



Stern CD, Bayly CI, Smith DGA, Fass J, Wang L-P, Mobley DL, and Chodera JD

Capturing non-local through-bond effects when fragmenting molecules for quantum chemical torsion scans

We show how the Wiberg Bond Order (WBO) can be used to construct small molecule fragmentation schemes that will avoid disrupting the chemical environment around torsions. The resulting fragmentation scheme powers the QCSubmit tool used to fragment and inject small molecule datasets into the QCFractal computation pipeline for deposition into the QCArchive quantum chemistry archive. The Open Force Field Initiative uses for constructing force fields, as well as powering bespoke torsion refitting for individual molecules.

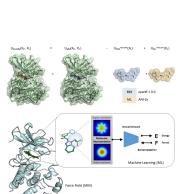


Preprint · arXiv

Mey ASJS[‡], 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

Best practices for alchemical free energy calculations

This living review for the Living Journal of Computational Molecular Sciences (LiveCoMS) covers the essential considerations for running alchemical free energy calculations for rational molecular design for drug discovery.



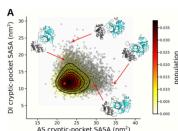
Preprint · bioRxiv

Rufa DA, Bruce Macdonald, HE, Fass J, Wieder M, Grinaway PB, Roitberg AE, Isayev O, and Chodera JD

Towards chemical accuracy for alchemical free energy calculations with hybrid physics-based machine learning / molecular mechanics potentials

In this first use of hybrid machine learning / molecular mechanics (ML/MM) potentials for alchemical free energy calculations, we demonstrate how the improved modeling of intramolecular ligand energetics offered by the quantum machine learning potential ANI-2x can significantly improve the accuracy in predicting kinase inhibitor binding free energy by reducing the error from 0.97 kcal/mol to 0.47 kcal/mol, which could drastically reduce the number of compounds that must be synthesized in lead optimization campaigns for minimal additional computational cost.

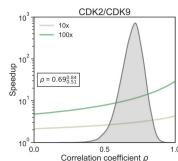
Preprint · bioRxiv



Zimmerman MI, Porter JR, Ward MD, Singh S, Vithani N, Meller A, Mallimadugula UL, Kuhn CE, Borowsky JH, Wiewiora RP, Hurley, MFD, Harbison AM, Fogarty CA, Coffland JE, Fadda E, Voelz VA[‡], Chodera JD[‡], Bowman GR[‡]
Citizen scientists create an exascale computer to combat COVID-19

To accelerate a multitude of drug development activities to combat the global threat posed by COVID-19, over a million citizen scientists have banded together through the Folding@home distributed computing project to create the world's first Exascale computer and simulate protein dynamics. An unprecedented 0.1 seconds of simulation of the viral proteome reveal how the spike complex uses conformational masking to evade an immune response, conformational changes implicated in the function of other viral proteins, and cryptic pockets that are absent in experimental structures. These structures and mechanistic insights present new targets for the design of therapeutics.

Preprint · bioRxiv



Albanese SK, Chodera JD, Volkamer A, Keng S, Abel R, and Wang L

Is structure based drug design ready for selectivity optimization?

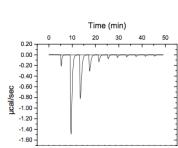
We asked whether the similarity of binding sites in related kinases might result in a fortuitous cancellation of errors in using alchemical free energy calculations to predict kinase inhibitor selectivities. Surprisingly, we find that even distantly related kinases have sufficient correlation in their errors that predicting changes in selectivity can be much more accurate than predicting changes in potency due to this effect, and show how this could lead to large reductions in the number of molecules that must be synthesized to achieve a desired selectivity goal.



Preprint · arXiv

Wang Y, Fass J, Stern CD, and Chodera JD
Graph nets for partial charge prediction

Graph convolutional and message-passing networks can be a powerful tool for predicting physical properties of small molecules when coupled to a simple physical model that encodes the relevant invariances. Here, we show the ability of graph nets to predict partial atomic charges for use in molecular dynamics simulations and physical docking.

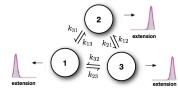


Preprint · bioRxiv

Boyce SE, Tellinghuisen JT, and Chodera JD

Avoiding accuracy-limiting pitfalls in the study of protein-ligand interactions with isothermal titration calorimetry

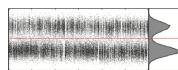
We demonstrate how to avoid accuracy-limiting problems in standard isothermal calorimetry experiments as well as capture the primary sources of uncertainty in thermodynamic parameters.



Preprint · arXiv

Chodera JD, Noé F, Hinrichs NS, Keller B, Elms PJ, Kaiser CM, Ewall-Wice A, Marqusee S, and Bustamante C
Bayesian hidden Markov model analysis of single-molecule biophysical experiments

We present a Bayesian hidden Markov model analysis scheme that allows biomolecular conformational dynamics—and the corresponding uncertainty due to limited data—to be inferred from single-molecule trajectories. This approach was developed for a single-molecule study examining folding dynamics of nascent proteins exiting the ribosome [Science 334:1723, 2011 · DOI].



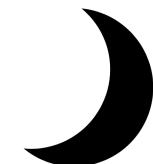
Preprint · arXiv

Chodera JD, Elms PJ, Swope WC, Prinz J-H, Marqusee S, Bustamante C, Noé F, and Pande VS

A robust approach to estimating rates from time-correlation functions

We present a simple, robust approach to estimating two-state rate constants from experimental or simulation data.

Published and In Press

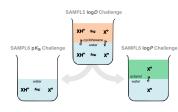


Nature Chemistry 12:581, 2020 · DOI

Chodera JD[‡], Lee AA[‡], London NJ[‡], and von Delft F[‡]

Crowdsourcing drug discovery for pandemics

The COVID-19 pandemic has left the world scrambling to find effective therapies to stem the tidal wave of death and put an end to the worldwide disruption caused by SARS-CoV-2. In this Correspondence, we argue for the need for a new open, collaborative drug discovery model (exemplified by our COVID Moonshot collaboration) that breaks free of the limitations of industry-led competitive drug discovery efforts that necessarily restrict information flow and hinder rapid progress by prioritizing profits and patent protection over human lives.



Journal of Computer Aided Molecular Design 34:335, 2020 · DOI

Isik M, Bergazin TD, Fox T, Rizzi A, Chodera JD, and Mobley DL

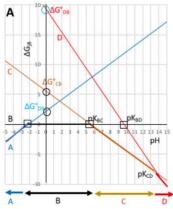
Assessing the accuracy of octanol-water partition coefficient predictions in the SAMPL6 Part II log P Challenge

We report the performance assessment of the 91 methods that were submitted to the SAMPL6 blind challenge for predicting octanol-water partition coefficient (logP) measurements. The average RMSE of the most accurate five MM-based, QM-based, empirical, and mixed approach methods based on RMSE were 0.92 ± 0.13 , 0.48 ± 0.06 , 0.47 ± 0.05 , and 0.50 ± 0.06 , respectively.

Journal of Computer Aided Molecular Design 34:561, 2020 · DOI

Gunner MR, Murakami T, Rustenburg AS, Isik M, Chodera JD

Standard state free energies, not pK_a s, are ideal for describing small molecule protonation and tautomeric states



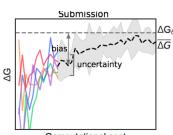
Here, we demonstrate how the physical nature of protonation and tautomeric state effects means that the standard state free energies of each microscopic protonation/tautomeric state at a single pH is sufficient to describe the complete pH-dependent microscopic and macroscopic populations. We introduce a new kind of diagram that uses this concept to illustrate a variety of pH-dependent phenomena, and show how it can be used to identify common issues with protonation state prediction algorithms. As a result, we recommend future blind prediction challenges utilize microstate free energies at a single reference pH as the minimal sufficient information for assessing prediction accuracy and utility.

Journal of Computer Aided Molecular Design 34:601, 2020 · DOI

Rizzi A, Jensen T, Slochower DR, Aldeghi M, Gapsys V, Ntekoumes D, Bosisio S, Papadourakis M, Henriksen NM, de Groot BL, Cournia Z, Dickson A, Michel J, Gilson MK, Shirts MR, Mobley DL, and Chodera JD

The SAMPL6 SAMPLing challenge: Assessing the reliability and efficiency of binding free energy calculations

To assess the relative efficiencies of alchemical binding free energy calculations, the SAMPL6 SAMPLing challenge asked participants to submit predictions as a function of computer effort for the same force field and charge model. Surprisingly, we found that most molecular simulation codes cannot agree on the binding free energy was, even for the same force field.



Journal of Computer Aided Molecular Design 34:405, 2020 · DOI

Isik M, Levorse D, Mobley DL, Rhodes T, and Chodera JD

Octanol-water partition coefficient measurements for the SAMPL6 Blind Prediction Challenge

We describe the design and data collection (and associated challenges) for the SAMPL6 part II $\log P$ octanol-water blind prediction challenge, where the goal was to benchmark the accuracy of force fields for druglike molecules (here, molecules resembling kinase inhibitors).

Journal of Chemical Theory and Computation 15:6225, 2019 · DOI

Slochower DR, Hendrikson NM, Wang LP, Chodera JD, Mobley DL, and Gilson MK

Binding thermodynamics of host-guest systems with SMIRNOFF99Frosst 1.0.5 from the Open Force Field Initiative

We assess the accuracy of the SMIRNOFF99Frosst 1.0.5 force field in reproducing host-guest binding thermodynamics in comparison with the GAFF force field, demonstrating how the SMIRNOFF format for compactly specifying force fields provide comparable accuracy with 20x fewer parameters.

Journal of Chemical Informatics and Modeling 59:4093, 2019 · DOI

Abraham MJ, Apostolov R, Barnoud J, Bauer P, Blau C, Bonvin AMMJ, Chavent M, Chodera JD, Condic-Jurkic K, Delemotte L, Grubmüller H, Howard RJ, Jordan J, Lindahl E, Ollila S, Selent J, Smith D, Stansfeld PJ, Tiemann J, Trellet M, Woods C, and Zhumov A

Sharing data from molecular simulations

There is a dire need to establish standards for sharing data in the molecular sciences. Here, we review the findings of a workshop held in Stockholm in Nov 2018 to discuss this need.

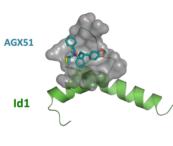


Cell Reports 29:62, 2019 · DOI

Wojnarowicz PM, Lima e Silva R, Ohnaka M, Lee SB, Chin Y, Kulukian A, Chang SH, Desai B, Escolano MG, Shah R, Garcia-Cao M, Xu S, Kadam R, Goldgur Y, Miller MA, Ouerfelli O, Yang G, Arakawa T, Albanese SK, Garland WA, Stoller G, Chaudhary J, Norton L, Soni RK, Philip J, Hendrickson RC, Iavarone A, Dannenberg AJ, Chodera JD, Pavletich N, Lasorella A, Campochiaro PA, Benezra R

A Small-Molecule Pan-Id Antagonist Inhibits Pathologic Ocular Neovascularization

We report the discovery and characterization of a small molecule, AGX51, with the surprising ability to inhibit the interaction of Id1 with E47, which leads to ubiquitin-mediated degradation of Ids.

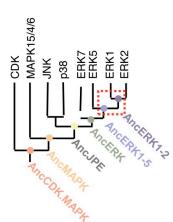


eLife, 2019;8:e38805 · DOI

Sang D, Pinglay S, Wiewiora RP, Selvan ME, Lou HJ, Chodera JD, Turk B, Gümüş Z, and Holt LJ

Ancestral reconstruction reveals mechanisms of ERK regulatory evolution

To understand how kinase regulation by phosphorylation emerged, we reconstruct the common ancestor of CDKs and MAPKs, using biochemical experiments and massively parallel molecular simulations to study how a few mutations were sufficient to switch ERK-family kinases from high- to low-autophosphorylation.



eLife 8:e45403, 2019 · DOI



Rafal P. Wiewiora[†], Shi Chen[†], Fanwang Meng, Nicolas Babault, Anqi Ma, Wenyu Yu, Kun Qian, Hao Hu, Hua Zou, Junyi Wang, Shijie Fan, Gil Blum, Fabio Pittella-Silva, Kyle A. Beauchamp, Wolfram Tempel, Hualing Jiang, Kaixian Chen, Robert Skene, Y. George Zheng, Peter J. Brown, Jian Jin, Chodera JD[‡], and Minkui Luo[‡]

The dynamic conformational landscapes of the protein methyltransferase SETD8

In this work, we show how targeted X-ray crystallography using covalent inhibitors and depletion of native ligands to reveal structures of low-population hidden conformations can be combined with massively distributed molecular simulation to resolve the functional dynamic landscape of the protein methyltransferase SETD8 in unprecedented atomistic detail. Using an aggregate of six milliseconds of fully atomistic simulation from Foldinghome, we use Markov state models to illuminate the conformational dynamics of this important epigenetic protein.

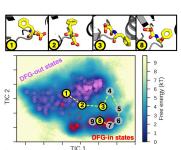


Nature Communications 10:2691, 2019 · DOI

Minuesa G, Albanese SK, Chow A, Schurer A, Park SM, Rotsides CZ, Taggart J, Rizzi A, Naden LN, Chou T, Gourkanti S, Cappel D, Passarelli MC, Fairchild L, Adura C, Glickman FJ, Schulman J, Famulare C, Patel M, Eibl JK, Ross GM, Tan DS, Leslie CS, Beeming T, Golgur Y, Chodera JD[‡], and Kharas MG.

Small-molecule targeting of MUSASHI RNA-binding activity in acute myeloid leukemia

We use absolute alchemical free energy calculations to identify the likely interaction site for a small hydrophobic ligand that shows activity against MUSASHI in AML.

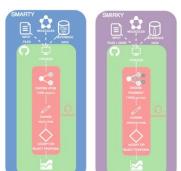


Cell Chemical Biology 26:390, 2019 · DOI

Hanson SM*, Georgiou G*, Miller WT, Rest JS, Chodera JD[‡], and Seeliger MA[‡]

What makes a kinase promiscuous for inhibitors?

Using a combination of chemogenomics, structural biology, and molecular simulation approaches, we identify a set of human kinases that are especially promiscuous binders of small molecule kinase inhibitors, and show that a prototypical member of this class, DDR1, achieves this promiscuity by virtue of its more stable Asp-DFG-out conformation.

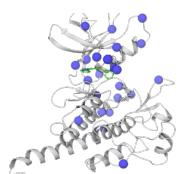


Journal of Chemical Theory and Computation 15:402, 2019 · DOI

Zanette C, Bannan CC, Bayly CI, Fass J, Gilson MK, Shirts MR, Chodera JD[‡], and Mobley DL

Toward learned chemical perception of force field typing rules

We show how machine learning can learn typing rules for molecular mechanics force fields within a Bayesian statistical framework.

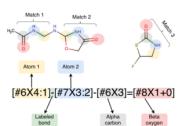


Communications Biology 1:70, 2018 · DOI

Hauser K, Negron C, Albanese SK, Ray S, Steinbrecher T, Abel R, and Chodera JD[‡], and Wang L

Predicting resistance of clinical Abl mutations to targeted kinase inhibitors using alchemical free-energy calculations

We show how alchemical free energy calculations can be used to predict whether clinical point mutations in human kinase domains confer resistance or susceptibility to targeted kinase inhibitors.



Journal of Chemical Theory and Computation 14:6076, 2018 · DOI

Mobley DL[‡], Bannan CC, Rizzi A, Bayly CI, Chodera JD[‡], Lim VT, Lim NM, Beauchamp KA, Shirts MR, Gilson MK, and Eastman PK

Escaping atom types using direct chemical perception with SMIRNOFF v0.1

We describe the philosophy behind a modern approach to molecular mechanics forcefield parameterization, and present initial results for the first SMIRNOFF-encoded forcefield: SMIRNOFF99Frosst.



Journal of Chemical Theory and Computation, in press · DOI

Swenson DWH, Prinz JH, Noé F, Chodera JD[‡], and Bolhuis PG

OpenPathSampling: A Python framework for path sampling simulations. I. Basics

To make powerful path sampling techniques broadly accessible and efficient, we have produced a new Python framework for easily implementing path sampling strategies (such as transition path and interface sampling) in Python. This first publication describes some of the theory and capabilities behind the approach.



Journal of Chemical Theory and Computation, in press · DOI

Swenson DWH, Prinz JH, Noé F, Chodera JD[‡], and Bolhuis PG

OpenPathSampling: A Python framework for path sampling simulations. II. Building and customizing path ensembles and sample schemes

To make powerful path sampling techniques broadly accessible and efficient, we have produced a new Python framework for easily implementing path sampling strategies (such as transition path and interface sampling) in Python. This second publication describes advanced aspects of the theory and details of how to customize path ensembles.



Journal of Computer Aided Molecular Design 32:937, 2018 · DOI

Rizzi A, Murkli S, McNeill J, Yao W, Sullivan M, Gilson MK, Chiu MW, Isaacs L, Gibb BC, Mobley DL‡, and Chodera JD ‡

Overview of the SAMPL6 host-guest binding affinity prediction challenge

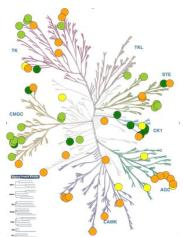
We present an overview of the host-guest systems and participant performance for the SAMPL6 host-guest blind affinity prediction challenges, assessing how well various physical modeling approaches were able to predict ligand binding affinities for simple ligand recognition problems where receptor sampling and protonation state effects are eliminated due to the simplicity of supramolecular hosts. We find that progress is now stagnated likely due to force field limitations.

Journal of Computer Aided Molecular Design 32:1117, 2018 · DOI

Isik M, Levorse D, Rustenburg AS, Ndukwie IE, Wang H, Reibarkh M, Martin GE, Makarov AA, Mobley DL, Rhodes T‡, and Chodera JD ‡

pKa measurements for the SAMPL6 prediction challenge for a set of kinase inhibitor-like fragments

The SAMPL5 blind challenge exercises identified neglect of protonation state effects as a major accuracy-limiting factor in physical modeling of biomolecular interactions. In this study, we report the experimental measurements behind a SAMPL6 blind challenges in which we assess the ability of community codes to predict small molecule pKas for small molecule resembling fragments of selective kinase inhibitors.

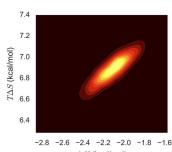


Biochemistry 57:4675, 2018 · DOI

Albanese SK*, Parton DL*, Isik M†, Rodríguez-Laureano L†, Hanson SM, Gradia S, Jeans C, Levinson NM, Seeliger M, and Chodera JD

An open library of human kinase domain constructs for automated bacterial expression

To establish a tractable experimental system for studying the biophysical determinants of selective kinase inhibitor resistance in clinical cancer mutations, we engineer a library of human kinase domains with useful bacterial expression with phosphatase coexpression.

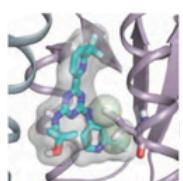


PLOS ONE 3(9): e0203224, 2018 · DOI

Nguyen TH, Rustenburg AS, Krimmer SG, Zhang H, Clark JD, Novick PA, Branson K, Pande VS, Chodera JD ‡, MinH DDL‡

Bayesian analysis of isothermal titration calorimetry for binding thermodynamics

We show how Bayesian inference can produce greatly improved estimates of statistical uncertainty from isothermal titration calorimetry (ITC) experiments, allowing the joint distribution of thermodynamic parameter uncertainties to be inferred.

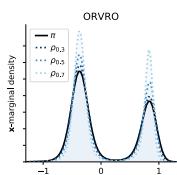


Nature 559:125, 2018 · DOI

Intlekofer AM*, Shih AH*, Wang B, Nazir A, Rustenburg AS, Albanese SK, Patel M, Famulare C, Correa FM, Arcila ME, Taylor J, Tallman MS, Roshal M, Petsko GA, Chodera JD, Thompson CB‡, Levine RL‡, Stein, EM‡

Acquired resistance to IDH inhibition through trans or cis dimer-interface mutations

Clinical double mutations acting in trans in cancer patients receiving IDH2 inhibitors act through a novel biophysical mechanism.

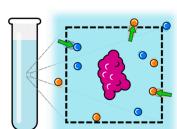


Entropy 20:318, 2018 · DOI

Fass J, Sivak DA, Crooks GE, Beauchamp KA, Leimkuhler B, and Chodera JD

Quantifying configuration-sampling error in Langevin simulations of complex molecular systems

We address a fundamental question regarding why molecular dynamics simulation works despite the fact that the use of finite timesteps leads to error in the sampled probability densities and populations, demonstrating how to measure configuration-space sampling error for an important class of Langevin integrators widely used in biomolecular simulation.



Journal of Physical Chemistry B 122:5466, 2018 · DOI

Ross GA, Rustenburg AS, Grinaway PB, Fass J, and Chodera JD

Biomolecular simulations under realistic salt conditions

We show how NCMC can be used to implement an efficient osmostat in molecular dynamics simulations to model realistic fluctuations in ion environments around biomolecules, and illustrate how the local salt environment around biological macromolecules can differ substantially from bulk.

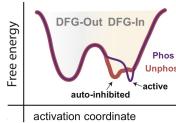


Journal of Physical Chemistry 122:5579, 2018 · DOI

Gill SC, Lim NM, Grinaway PB, Rustenburg AS, Fass J, Ross GA, Chodera JD, and Mobley DL

Binding Modes of Ligands Using Enhanced Sampling (BLUES): Rapid Decorrelation of Ligand Binding Modes Using Nonequilibrium Candidate Monte Carlo

Nonequilibrium candidate Monte Carlo can be used to accelerate the sampling of ligand binding modes by orders of magnitude over instantaneous Monte Carlo.

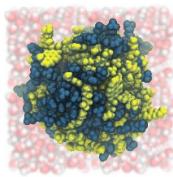


eLife 7:e32766, 2018 · DOI

Ruff EF, Muretta JM, Thompson A, Lake E, Cyphers S, Albanese SK, Hanson SM, Behr JM, Thomas DT, Chodera JD, and Levinson NM

A dynamic mechanism for allosteric activation of Aurora kinase A by activation loop phosphorylation

Through a combination of FRET, IR, and EPR labeling and large-scale molecular dynamics simulations, we show that phosphorylation activates Aurora kinase by a novel mechanism that does not simply correspond to a DFG-out to DFG-in population shift, but rather reorganization of DFG-in subpopulations.

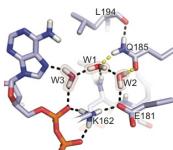


Nature Materials 17:361, 2018 · DOI

Shamay Y, Shah J, Tschaharganeh DF, Roxbury D, Budhathoki-Uprety J, Ijsik M, Mizrahi A, Nawaly K, Sugarman JL, Baut E, Neiman MR, Johnson DC, Sridharan R, Chu KL, Rajasekhar VK, Chodera JD, Lowe SW, and Heller DA

Quantitative self-assembly prediction yields targeted nanoparticles

A decision tree based on predicted physical properties and molecular descriptors is capable of predicting the assembly of drug/dye nanoparticles that can be used in tumor-targeted selective kinase inhibitor therapy to minimize on- and off-pathway toxicity.

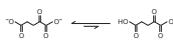


Nature Chemical Biology 13:402, 2017 · DOI

Cyphers S, Ruff E, Behr JM, Chodera JD, and Levinson NM

A conserved water-mediated hydrogen bond network governs allosteric activation in Aurora kinase A

Over 50 microseconds of aggregate simulation data on Folding@home reveal a surprisingly stable hydrogen bond network underlies allosteric activation by Tpx2.

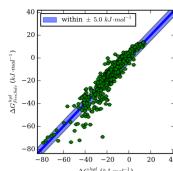


Nature Chemical Biology 13:494, 2017 · DOI

Intlekofer A, Wang B, Liu H, Shah H, Carmona-Fontaine C, Rustenburg AS, Salah S, Gunner MR, Chodera JD, Cross JR, and Thompson CB

Acidification enhances production of L-2-hydroxyglutarate through alternative substrate use by dehydrogenase enzymes

At low pH, metabolic enzymes lactate dehydrogenase and malate dehydrogenase undergo shifts in substrate utilization that have high relevance to cancer metabolism due to surprisingly simple protonation state effects.



Journal of Chemical & Engineering Data 62:1559, 2017 · DOI

Matos GDR, Kyu DY, Loeffler HH, Chodera JD, Shirts MR, and Mobley DL

Approaches for calculating solvation free energies and enthalpies demonstrated with an update of the FreeSolv database

We review alchemical approaches to computing solvation free energies and update FreeSolv—the most popular database of hydration free energies of neutral molecules—with more computed and experimental properties.

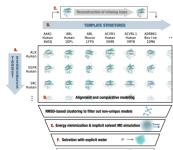


PLoS Computational Biology 13:e1005659, 2017 · DOI

Eastman P, Swails J, Chodera JD, McGibbon RT, Zhao Y, Beauchamp KA, Wang LP, Simmonett AC, Harrigan MP, Brooks BR, and Pande VS

OpenMM 7: Rapid development of high performance algorithms for molecular dynamics

The latest version of the GPU-accelerated molecular simulation OpenMM features a variety of incredibly flexible but fast tools for rapidly prototyping, evaluating, and deploying new simulation algorithms.



PLoS Computational Biology 12:e1004728, 2016 · DOI

Parton DL, Grinaway PB, Hanson SM, Beauchamp KA, and Chodera JD

Ensembler: Enabling high-throughput molecular simulations at the superfamily scale

We demonstrate a new tool that enables—for the first time—massively parallel molecular simulation studies of biomolecular dynamics at the superfamily scale, illustrating its application to protein tyrosine kinases, an important class of drug targets in cancer.

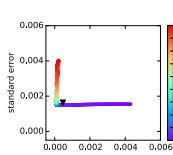


Journal of Clinical Investigation 126:3529, 2016 · DOI

Xu J, Pham CG, Albanese SK, Dong Y, Oyama T, Lee CH, Rodrik-Outmezguine V, Yao Z, Han S, Chen D, Parton DL, Chodera JD, Rosen N, Cheng EH, and Hsieh JJ

Mechanistically distinct cancer-associated mTOR activation clusters predict sensitivity to rapamycin

We use massively parallel distributed molecular simulations on Folding@home to probe the mechanism activating mutations of the mTOR kinase identified in clinical populations.



Journal of Chemical Theory and Computation 12:1799, 2016 · DOI

Chodera JD

A simple method for automated equilibration detection in molecular simulations

We present a simple approach to automatically determining the equilibrated region of a molecular simulation, a longstanding challenge formerly without a good solution.

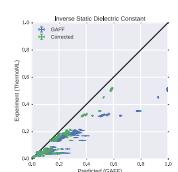


Journal of Computer Aided Molecular Design, 30:945, 2016 · DOI

Rustenburg AS, Dancer J, Lin B, Ortwinne D, Mobley DL, and Chodera JD

Measuring cyclohexane-water distribution coefficients for the SAMPL5 challenge

To test the accuracy of physical modeling techniques in predicting free energies of transfer between aqueous and nonpolar solvents, we worked with Genentech to develop a new protocol to measure cyclohexane-water distribution coefficients for 53 druglike compounds at pH 7.4, fielding a blind community challenge as part of the [SAMPL5 exercise](#). A special issue of JCAMD was published with 16 papers describing various approaches used by participants to predict this data and understand their failures.

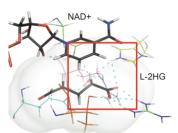


Journal of Physical Chemistry B 119:12912, 2015 · DOI

Beauchamp KA, Behr JM, Rustenburg AS, Bayly CI, Kroenlein K, and Chodera JD

Towards automated benchmarking of atomistic forcefields: Neat liquid densities and static dielectric constants from the ThermoML data archive

Molecular mechanics forcefields are critical to computer-guide drug design, but the benchmarking and improvement of these forcefields has been hindered by the lack of high-quality machine-readable physical property datasets. We show how the NIST-curated ThermoML Archive, which stores physical property data in an IUPAC-standard XML format, can eliminate these roadblocks and reveal issues with current generation forcefields.

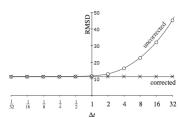


Cell Metabolism 22:1–8, 2015 · DOI

Intlekofer AM, Dematteo RG, Venetti S, Finley LWS, Lu Chao, Judkins AR, Rutenburg AS, Grinaway PB, Chodera JD, Cross JR, and Thompson CB

Hypoxia introduces production of L-2-Hydroxyglutarate

Molecular docking is used to demonstrate the potential for alternative substrate usage by isocitrate dehydrogenases under hypoxic conditions in cancer.

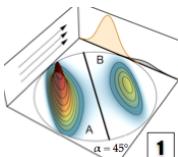


Journal of Physical Chemistry B, 118:6466–6474, 2014. William C. Swope Festschrift · DOI

Sivak DA, Chodera JD, and Crooks GE

Time step rescaling recovers continuous-time dynamical properties for discrete-time Langevin integration of nonequilibrium systems

We derive a simple, easy-to-implement Langevin integrator that has universally useful properties in molecular simulations.

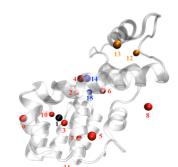


Physical Review X 4:011020, 2014 · DOI

Prinz J-H, Chodera JD, and Noé F

Spectral rate theory for two-state kinetics

We present a new mathematical framework for unifying various two-state rate theories presented in the physical chemistry literature over many decades, and provide a quantitative way to measure reaction coordinate quality.

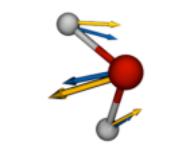


Journal of Computer Aided Molecular Design 27:989–1007, 2013 · DOI

Wang K, Chodera JD, Yang Y, and Shirts MR

Identifying ligand binding sites and poses using GPU-accelerated Hamiltonian replica exchange molecular dynamics

We show how bound ligand poses can be identified even when the location of the binding sites are unknown using the machinery of alchemical modern free energy calculations on graphics processors.

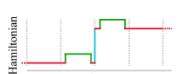


Journal of Physical Chemistry B 117:9956–9972, 2013 · DOI

Wang L-P, Head-Gordon TL, Ponder JW, Ren P, Chodera JD, Eastman PK, Martinez TJ, and Pande VS

Systematic improvement of a classical molecular model of water

Water is the most important molecule in biology, and accurate treatment of its interactions is critical to accurate modeling for drug discovery. While polarizable models of water can achieve very high accuracies, they are both difficult to parameterize and expensive to employ. Here, we show how a high quality inexpensive polarizable model of liquid water can be derived using an automated parameterization engine.



Physical Review X 3:011007, 2013 · DOI

Sivak DA, Chodera JD, and Crooks GE

Using nonequilibrium fluctuation theorems to understand and correct errors in equilibrium and nonequilibrium discrete Langevin dynamics simulations

All molecular dynamics simulations introduce error into the sampled distribution by virtue of the finite timestep used to integrate the equations of motion on a digital computer. While traditional approaches to analyzing this error are extremely complicated, we show how interpreting finite-timestep integrators as a form of nonequilibrium driving leads to simple, straightforward schemes for assessing the impact of these errors, as well as correcting for them.

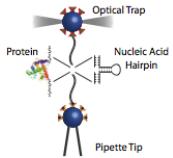


Journal of Chemical Theory and Computation 9:461, 2012 · DOI

Eastman P, Friedrichs MS, Chodera JD, Radmer RJ, Bruns CM, Ku JP, Beauchamp KA, Lane TJ, Wang L, Shukla D, Tye T, Houston M, Stich T, Klein C, Shirts MR, and Pande VS

OpenMM 4: A reusable, extensible, hardware independent library for high performance molecular simulation

Inexpensive consumer GPUs promise a 100-fold increase in simulation power by problems that can effectively exploit their highly specialized structure. Here, we describe the latest advances in an extremely high performance, open-source, extensible GPU-accelerated library and toolkit for molecular simulation.

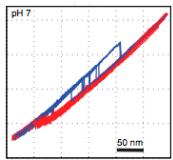


Biophysical Journal 103:1490, 2012 · DOI

Elms PJ, Chodera JD, Bustamante CJ, Marqusee S

The limitations of constant-force-feedback experiments

Popular constant-force-feedback single-molecule experiments can cause severe artifacts in single-molecule force spectroscopy data. We demonstrate a simple alternative that eliminates these artifacts.



Proceedings of the National Academy of Sciences 109:3796, 2012 · DOI

Elms PJ, Chodera JD, Bustamante C, Marqusee S

The molten globule state is unusually deformable under mechanical force

We measure the physical properties of the molten globule state of apo-myoglobin, and show that it is unusually deformable compared to typical protein native states.

$$f_{\text{exp}} = \int d\vec{r} f(\vec{r}) p_1(\vec{r})$$

Journal of Chemical Theory and Computation 8:3445, 2012 · DOI

Pitera JW and Chodera JD

On the use of experimental observations to bias simulated ensembles

We show how the concept of maximum entropy can be used to recover unbiased conformational distributions from experimental data, and how this concept relates to the popular 'ensemble refinement' schemes for NMR data analysis.

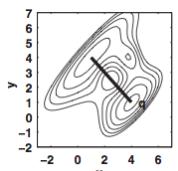


Science 334:1723, 2011 · DOI

Kaiser CM, Goldman DH, Chodera JD, Tinoco I, Jr., and Bustamante C

The ribosome modulates nascent protein folding

Using single-molecule force spectroscopy, we show how the ribosome itself modulates the folding dynamics of nascent protein chains emerging from the exit tunnel.

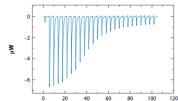


Physical Review Letters 107:098102, 2011 · DOI

Chodera JD and Pande VS

Splitting probabilities as a test of reaction coordinate choice in single-molecule experiments

We demonstrate a simple test for identifying poor reaction coordinates in single-molecule experiments.

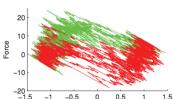


Analytical Biochemistry 414:297, 2011 · DOI

Tellinghuisen JT and Chodera JD

Systematic errors in isothermal titration calorimetry: Concentrations and baselines

A word of caution about large errors in isothermal titration calorimetry measurements arising from ligand concentration errors.

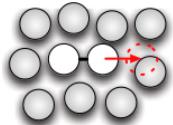


Journal of Chemical Physics 134:024111, 2011 · DOI

Minh DDL, Chodera JD

Estimating equilibrium ensemble averages using multiple time slices from driven nonequilibrium processes: Theory and application to free energies, moments, and thermodynamic length in single-molecule pulling experiments

We derive a new estimator for estimating equilibrium expectations from nonequilibrium experiments, and show how it can be used to estimate a variety of useful quantities in simulated single-molecule force spectroscopy experiments.

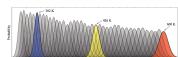


Proceedings of the National Academy of Sciences 108:E1009, 2011 · DOI

Nilmeier JP, Crooks GE, Minh DDL, and Chodera JD

Nonequilibrium candidate Monte Carlo is an efficient tool for equilibrium simulation

We present a significant generalization of Monte Carlo methods that provide an enormously useful tool for enhancing the efficiency of molecular simulations and enabling molecular design.

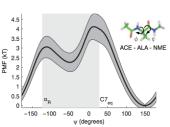


Journal of Chemical Physics 134:244108, 2011 · DOI

Prinz J-H, Chodera JD, Pande VS, Smith JC, and Noé F

Optimal use of data in parallel tempering simulations for the construction of discrete-state Markov models of biomolecular dynamics

We demonstrate how multitemperature data from parallel tempering simulations can be used to construct fully temperature-dependent models of the dynamics of biomolecular systems.

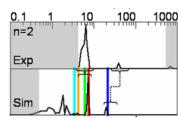


Journal of Chemical Physics 134:244107, 2011 · DOI

Chodera JD, Swope WC, Noé F, Prinz J-H, Shirts MR, and Pande VS

Dynamical reweighting: Improved estimates for dynamical properties from simulations at multiple temperatures

We describe how reweighing techniques can provide optimal estimates of temperature-dependent dynamical properties from simulations conducted at multiple temperatures.

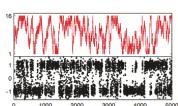


Proceedings of the National Academy of Sciences 108:4822, 2011 · DOI

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

We present a new framework for comparing essential features of the dynamics between experiment and simulation to identify the kinetics processes contributing to individual relaxation timescales in perturbation-response or correlation spectroscopy experiments.

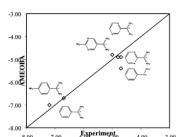


Journal of Chemical Physics 135:194110, 2011 · DOI

Chodera JD and Shirts MR

Replica exchange and expanded ensemble simulations as Gibbs sampling: Simple improvements for enhanced mixing

We show how a simple change to the way exchanges are handled in the popular replica-exchange simulation methodology can astronomically increase efficiency at no increase in computational cost.

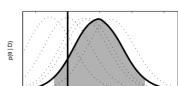


Journal of Physical Chemistry B 114:2549, 2010 · DOI

Ponder JW, Wu C, Ren P, Pande VS, Chodera JD, Mobley DL, Schnieders MJ, Haque I, Lambrecht DS, DiStasio RA Jr., Head-Gordon M, Clark GN, Johnson ME, and Head-Gordon T

Current status of the AMOEBA polarizable force field

The AMOEBA polarizable force field is able to reproduce a diverse set of physical chemical phenomenon to high accuracy.



Journal of Chemical Physics 133:105102, 2010 · DOI

Chodera JD and Noé F

Probability distributions of molecular observables computed from Markov models.

II. Uncertainties in observables and their time-evolution

A simple Bayesian approach for the modeling of statistical uncertainties in kinetic and equilibrium quantities computed from Markov state models of biomolecular dynamics.

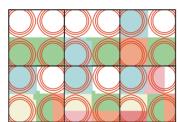


Biophysical Journal 98:3062, 2010 · DOI

Adelman JL, Chodera JD, Kuo IW, Miller TF, and Barsky D

The mechanical properties of PCNA: Implications for the loading and function of a DNA sliding clamp

Molecular simulations of the PCNA clamp responsible for DNA polymerase processivity show a surprisingly small energetic penalty for the deformation required for clamp loading. Featured on issue cover.

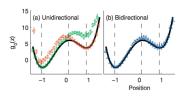


Journal of Chemical Physics 131:045106, 2009 · DOI

Bacallado S, Chodera JD, and Pande VS

Bayesian comparison of Markov models of molecular dynamics with detailed balance constraint

A Bayesian scheme for comparing state space decompositions for Markov state models of biomolecular dynamics that incorporates the fact that physical systems must obey detailed balance. This paper utilizes recent results from Markov chain theory on edge-reinforced random walks.



Journal of Chemical Physics 131:134110, 2009 · DOI

Minh DDL, Chodera JD

Optimal estimators and asymptotic variances for nonequilibrium path-ensemble averages

We derive an optimal estimator and corresponding statistical uncertainties for inferring expectations of bidirectional nonequilibrium processes. These estimators have widespread applicability in single-molecule biophysical force-spectroscopy experiments and nonequilibrium molecular simulations.

Journal of Chemical Physics 129:124105, 2008 · DOI

Shirts MR, Chodera JD

Statistically optimal analysis of samples from multiple equilibrium states

We present a highly general, statistically optimal approach for producing estimates of free energies and equilibrium expectations from multiple simulations that provably extracts all useful information from the data.



Journal of Medicinal Chemistry 51:769, 2008 · DOI

Nicholls A*, Mobley DL*, Guthrie JP, Chodera JD, and Pande VS

Predicting small-molecule solvation free energies: A blind challenge test for computational chemistry

A blind evaluation of the accuracy of alchemical free energy methods for computing gas-to-water transfer free energies (solvation free energies) of small molecules demonstrates that modern forcefields are likely sufficiently accurate to be useful in drug design.

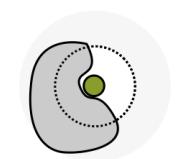


Journal of Physical Chemistry B 112:938, 2008 · DOI

Mobley DL, Dill KA, and Chodera JD

Treating entropy and conformational changes in implicit solvent simulations of small molecules

An quantitative examination of how much conformational entropy contributes to hydration free energies of small molecules, with implications for ligand binding.

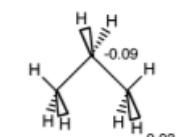


Journal of Physical Chemistry B 111:13052, 2007 · DOI

Shirts MR*, Mobley DL*, Chodera JD, and Pande VS

Accurate and efficient corrections for missing dispersion interactions in molecular simulations

We identify a major source of systematic error in absolute alchemical free energy calculations of ligand binding and show how a simple procedure can inexpensively and accurately eliminate it.



Journal of Physical Chem B 111:2242, 2007 · DOI

Mobley DL, Dumont E, Chodera JD, Bayly CI, Cooper MD, and Dill KA

Comparison of charge models for fixed-charge force fields: Small-molecule hydration free energies in explicit solvent

We compare a number of popular methods for deriving charge models for small molecules, deriving lessons about best practices for accurate simulations.

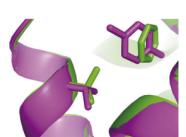


Journal of Molecular Biology 371:1118, 2007 · DOI

Mobley DL, Graves AP, Chodera JD, McReynolds AC, Shoichet BK, and Dill KA

Predicting absolute ligand binding free energies to a simple model site

We show how alchemical free energy calculations are capable of accurate blind prediction of small-molecule binding affinities to a simple model protein binding site.



Journal of Chemical and Theoretical Computation 3:1231, 2007 · DOI

Mobley DL, Chodera JD, and Dill KA

Confine-and-release method: Obtaining correct binding free energies in the presence of protein conformational change

We present a general scheme for obtaining correct ligand binding affinities when protein conformational change is implicated in ligand binding.



Journal of Chemical Physics 126:155101, 2007 · DOI

Chodera JD*, Singhal N*, Swope WC, Pitera JW, Pande VS, and Dill KA

Automatic discovery of metastable states for the construction of Markov models of macromolecular conformational dynamics

Proposing one of the first automated algorithms for discovering kinetically metastable states of biomolecules from molecular simulations, this paper shows how many biomolecules can possess numerous distinct long-lived conformational states even though the equilibrium populations of these states may too small for standard structural biology techniques to detect.

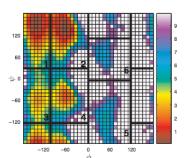


Proceedings of the National Academy of Sciences 104:11987, 2007 · DOI

Ozkan SB, Wu GA, Chodera JD, and Dill KA

Protein Folding by Zipping and Assembly

A review of the utility of the proposed zipping and assembly mechanism for the concomitant formation of secondary and tertiary structure in protein folding for predicting folding pathways and native structures.

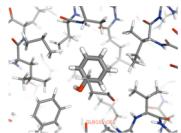


Journal of Chemical Theory and Computation 3:26, 2007 · DOI

Chodera JD, W. C. Swope, J. W. Pitera, C. Seok, and K. A. Dill

Use of the weighted histogram analysis method for the analysis of simulated and parallel tempering simulations

The weighted histogram analysis method (WHAM), a mainstay of molecular dynamics simulation analysis, is thoroughly explained and modernized for the analysis of simulated and parallel tempering simulation data.

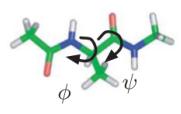


Journal of Chemical Physics 125:084902, 2006 · DOI

Mobley DL, Chodera JD, and Dill KA

On the use of orientational restraints and symmetry corrections in alchemical free energy calculations

We illustrate how orientational restraints can be used to greatly reduce the computational effort in alchemical calculations of ligand binding free energies, and clarify how symmetry corrections are necessary when molecules contain symmetric or pseudosymmetric substituents.

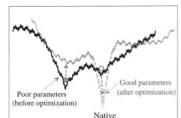


Multiscale Modeling and Simulation 5:1214, 2006 · DOI

Chodera JD, Swope WC, Pitera JW, and Dill KA

Long-time protein folding dynamics from short-time molecular dynamics simulations

We show how the long-time dynamics of biomolecular systems can be recapitulated from statistics collected from short molecular simulations sampling transitions between kinetically metastable states.

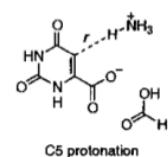


Journal of Computational Chemistry 24:89, 2003 · DOI

Seok C, Rosen JB, Chodera JD, Dill KA

MOPED: Method for optimizing physical energy parameters using decoys

We propose a new way to optimize parameters for a physical energy function using decoy structures for protein folding studies.



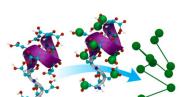
Journal of the American Chemical Society 123:12837, 2001 · DOI

Lee TS*, Chong LT*, Chodera JD, and Kollman PA

An alternative explanation for the catalytic proficiency of orotidine 5'-phosphate decarboxylase

A combined QM and MD analysis of potential plausible mechanisms to explain the enormous catalytic acceleration of one of the most proficient enzymes known.

Reviews and Commentaries

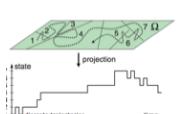


Journal of Chemical Theory and Computation · DOI

Gkeka P, Stoltz G, Farimani AB, Belkacemi Z, Ceriotti M, Chodera JD, Dinner AR, Ferguson A, Maillet JB, Minoux H, Peter C, Pietrucci F, Silveira A, Tkatchenko A, Trstanova Z, Wiewiora R, Leliévre T

Machine learning force fields and coarse-grained variables in molecular dynamics: application to materials and biological systems

We review the state of the art in applying machine learning to coarse grain force fields in space and time to study multiscale dynamics.

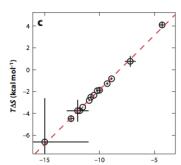


Current Opinion in Structural Biology 25:135, 2014 · DOI

Chodera JD and Noé F

Markov state models of biomolecular conformational dynamics

A review of exciting recent developments in the stochastic modeling of biomolecular dynamics using techniques I originally co-developed to study protein folding.

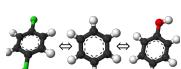


Annual Reviews in Biophysics 42:121, 2013 · DOI

Chodera JD and Mobley DL

Entropy-enthalpy compensation: Role and ramifications for rational ligand design

Entropy-enthalpy compensation is likely a universal phenomena, but not as severe as widely thought, and irrelevant for drug discovery and ligand design.

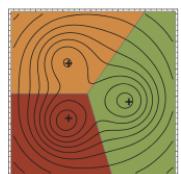


Current Opinion in Structural Biology 21:150, 2011 · DOI

Chodera JD, Mobley DL, Shirts MR, Dixon RW, Branson KM, and Pande VS

Free energy methods in drug discovery and design: Progress and challenges

A review of current opportunities and challenges for alchemical free energy calculations in drug discovery and design.

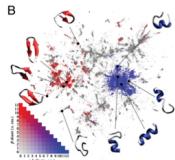


Journal of Chemical Physics 134:174105, 2011 · DOI

Prinz JH, Wu H, Sarich M, Keller B, Fischbach M, Held M, Chodera JD, Schütte, and Noé F

Markov models of molecular kinetics: Generation and validation

Current best practices for the generation and validation of Markov state models for describing the stochastic dynamics of biomolecular systems.

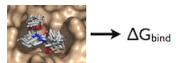


Proceedings of the National Academy of Sciences 108:12969, 2011 · DOI

Chodera JD and Pande VS

The Social Network (of protein conformations)

A new methodology for mapping protein conformational spaces is reminiscent of how we use two-dimensional maps to navigate a three-dimensional world.

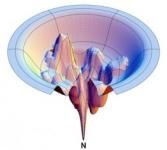


Annual Reports in Computational Chemistry 3:41, 2007 · DOI

Shirts MR, Mobley DL, Chodera JD

Alchemical free energy calculations: Ready for prime time?

A review of current alchemical free energy methodologies and their potential for use in drug discovery and ligand design.



Current Opinion in Structural Biology 17(3):342, 2007 · DOI

Dill KA, Ozkan SB, Weikl TR, Chodera JD, and Voelz VA

The protein folding problem: When will it be solved?

A review of the current state of the protein folding problem.

Scientific Advisory Boards

2013–2018
2018–

Schrödinger, LLC
OpenEye Scientific

Peer reviewer for scientific journals

Bioinformatics, Biopolymers, Chemical Physics, Computation, Drug Discovery Today, European Biophysics Journal, Entropy, International Journal of Molecular Sciences, Journal of the American Chemical Society, Journal of Chemical Theory and Computation, Journal of Computer-Aided Molecular Design, Journal of Computational Chemistry, Journal of Computational Physics, Journal of Physical Chemistry, Journal of Physical Chemistry Letters, Molecular Physics, Multiscale Modeling & Simulation, Nature Chemistry, Nature Communications, Nature Physics, Pacific Symposium in Biocomputing, PLoS Computational Biology, PLoS One, Proceedings of the National Academy of Sciences, Science, Scientific Reports, Structure

Service

2018–
2012–2015

Open Force Field Consortium Governing Board
<http://openforcefield.org/consortium>
MSKCC High Performance Computing Steering Committee
Member, Co-founder

Graduate Programs

2013–
2013–
2013–
2015–

Program in Physiology, Biophysics, and Systems Biology (PPSB)
Tri-Institutional PhD Program in Chemical Biology (TPCB)
Tri-Institutional Program in Computational Biology and Medicine (CBM)
Gerstner Sloan Kettering Graduate Program (GSK)

Teaching

Virginia Tech
Summer 2017

Tri-I
2015-2018

WCMC
2018-

MolSSI Software Summer School Instructor
Molecular Software Sciences Institute
CBM Journal Club Moderator
Tri-I Computational Biology and Medicine Program
BCMB Biochemistry
WCMC Graduate School of Medical Sciences (statistical mechanics and thermodynamics unit)

Grant Reviews and Study Sections

NIH

Macromolecular Structure and Function B [MSFB] (*early career reviewer*)

NSF

Ad hoc reviewer and virtual panel member for Chemical Theory, Models, and Computational Methods (CTMC)

Conferences organized

London, UK
Sep 2019

CompBioMed 2019
IET London
MolKin 2019: Molecular Kinetics: Sampling, Design and Machine Learning
Freie Universität Berlin, Germany

Göttingen, Germany
May 2019

Alchemical Free Energy Methods Workshop
Novartis, Cambridge, MA

Boston, MA
May 2018

Free Energy Methods and Molecular Kinetics in Drug Design Workshop
Novartis, Cambridge, MA

San Francisco, CA
Sep 2017

MolSSI Workshop on Workflows in Biomolecular Simulation
Autodesk

Berkeley, CA
Jan 2017

SMML//2017: Statistical Mechanics // Machine Learning
University of California, Berkeley

Boston, MA
May 2016

Free Energy Methods in Drug Design Workshop
Vertex Pharmaceuticals, Boston, MA

Cambridge, MA
May 2016

Markov State Models in Drug Design Workshop
Novartis, Cambridge, MA

Berlin, Germany
Sep 2015

World Molecular Kinetics Workshop 2015
Freie Universität Berlin, Germany

Boston, MA
May 2014

Free Energy Methods in Drug Design Workshop
Vertex Pharmaceuticals, Boston, MA

Berlin, Germany
Sep 2013

World Molecular Kinetics Workshop 2013
Freie Universität Berlin, Germany

Cambridge, MA
May 2012

Free Energy Methods in Drug Design Workshop
Vertex Pharmaceuticals, Cambridge, MA

Berlin, Germany
Sep 2011

World Molecular Kinetics Workshop 2011
Freie Universität Berlin, Germany

Cambridge, MA
May 2010

Free Energy Methods in Drug Design Workshop
Vertex Pharmaceuticals, Cambridge, MA

Berlin, Germany
May 2009

World Molecular Kinetics Workshop 2009
Freie Universität Berlin, Germany

Funding

All funding sources are publicly available online at <http://choderalab.org/funding>

Active

Single-Investigator Grants

NIH R01 GM121505

The role of reorganization energy in achieving selective kinase inhibition

The goal of this project is to probe the role of protein reorganization energy in achieving selectivity in targeted kinase inhibition with small molecules.

9/1/2017 – 8/31/2022

\$196,250 annual direct costs

Vir Biosciences Sponsored Research Agreement SK2019-0582

Development of alchemical free energy methods for predicting the impact of point mutations

The goal of this project is to develop alchemical free energy methods for predicting the impact of point mutations on antibody:antigen affinities.

7/25/19 – 7/24/2021

\$55,556 annual direct costs to the Chodera lab

Relay Therapeutics Collaboration SK2018-0162 Amendment 2

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 alchemical free energy calculations, as well as Bayesian integrative modeling techniques for experimental biophysical data and molecular simulations.

3/1/2020 – 4/5/2021

\$124,828 annual direct costs to the Chodera lab

Bayer Sponsored Research Agreement SK2019-1289

Development of a combined machine learning / alchemical free energy approach to predict the impact of mutations on small molecule kinase inhibitor binding

The goal of this project is to develop open source scalable free energy and machine learning workflows to predict which mutations of kinases small molecule therapeutics may be effective against.

3/1/2020 – 4/5/2021

\$117,105 annual direct costs to the Chodera lab

Collaborative Grants

NIH R01 1R01GM132386 (PIs: John Chodera, MSKCC and Michael Shirts, University of Colorado)

Open data-driven infrastructure for building biomolecular force fields for predictive biophysics and drug design

co-Is: David Mobley (UCI), Lee-Ping Wang (UC Davis), Michael Gilson (UCSD)

The goal of this project is to develop a modern open infrastructure for building fully consistent biopolymer and small molecule force fields for drug design and predictive biophysical modeling.

6/1/2019 – 5/30/2023

\$105,000 annual direct costs to the Chodera lab

NIH R01 GM124270 (PI: David Mobley, UCI)

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

The goal of this project is to enable blind community challenges that drive progress toward quantitative accuracy in the field of computational physical modeling of drug-receptor interactions.

9/10/2018 – 8/31/2022

\$57,588 annual direct costs to the Chodera lab

NSF CHI 1904822 (PI: David Minh, IIT)

Collaborative Research: CDS&E: Elucidating Binding using Bayesian Inference to Integrate Multiple Data Sources

The goal of this project is to develop a scalable approach to Bayesian inference from biophysical experiments

9/1/2019 – 8/31/2022

\$47,237 annual direct costs to the Chodera lab

Functional Genomics Initiative (FGI)

Integrated Approaches Annotate Functions of Cancer-associated H3K36 Methyltransferases

The goal of this project is to develop approaches for using large-scale physical modeling and biochemical experiments to annotate the functions of clinical cancer mutations.

1/1/2019 – 12/31/2020

co-PI: Minkui Luo

\$125,000 annual direct costs to the Chodera lab

BIH Einstein Visiting Professorship at the Charité Berlin

Computational polypharmacology: A new paradigm for selectively promiscuous kinase inhibitors

The goal of this project is to develop structure-informed machine learning approaches to predicting kinase inhibitor polypharmacology for computer-guided small molecule design.

1/1/2019 – 12/31/2021

EUR150,000 annual direct costs to Chodera (via Charité) for Berlin working group

Fellowships

Karmen Čondić-Jurkić, Postdoctoral Research Fellow

Open Force Field Consortium Postdoctoral Fellowship

4/1/2020 – 3/31/2021

\$88,864.10 stipend, supplies, and travel support

Ivy Zhang CBM Graduate Student

MolSSI COVID-19 Seed Software Fellowship

7/1/2020 – 12/31/2020

\$20,000/year stipend support

Hannah Bruce Macdonald, Postdoctoral Fellow

MolSSI Investment Software Fellowship

7/1/2019 – 12/31/2020

\$50,000/year stipend support

Pending

Single-Investigator Grants and Contracts

(Note: JDC has already reached the NIH GMS limit of two funded grants on which he serves as Principal Investigator.)

Foresite Labs Sponsored Research Agreement

Predicting the binding of cancer-associated substrates to ubiquitin ligases

The goal of this project is to develop and apply open source tools to predict the binding of cancer-associated substrates to ubiquitin ligases.

8/1/2020 – 7/30/2022

\$119,500 annual direct costs to the Chodera lab

Silicon Therapeutics Sponsored Research Agreement

Investigating the efficiency of algorithms for relative free energy calculations

The goal of this project is to assess the relative efficiencies of various algorithms for relative free energy calculations for drug discovery.

9/1/2020 – 8/31/2022

\$94,680 annual direct costs to the Chodera lab

Collaborative Grants

NIH COVID-19 R01 1R01AI161245 (PI: John Chodera, MSKCC)

Development of small molecule SARS-CoV-2 Mpro inhibitors via large-scale crystallography and computation

co-Is: Frank von Delft (Oxford), Annette von Delft (Oxford), Nir London (Weizmann)

The goal of this project is to develop a small molecule inhibitor for SARS-CoV-2 Mpro using a combination of large-scale free energy calculations and high-throughput X-ray crystallography.

9/1/2020 – 8/31/2023

\$292,186 annual direct costs to the Chodera lab

NIH 1R01GM140090 (PI: Tom Markland, Stanford University)

OpenMM: Scalable biomolecular modeling, simulation, and machine learning

co-I: Gianni de Fabritiis (Universitat de Pompeu Fabra, Barcelona)

The goal of this project is to support continued development of OpenMM, transition to a community governance and distributed development model, and extension to integrate physical and machine learning models to enable genomic-scale biomolecular modeling, simulation, and prediction.

9/1/2020 – 8/31/2024

\$95,000 annual direct costs to the Chodera lab

Fellowships

None

Completed

Single-Investigator Grants and Contracts

Relay Therapeutics Sponsored Research Agreement SK2018-0162

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, as well as Bayesian integrative modeling techniques for experimental biophysical data and molecular simulations.

4/5/2018 – 4/5/2019

\$74,074 annual direct costs to the Chodera lab

Entasis Therapeutics Sponsored Research Agreement SK2018-0163

Development of efficient equilibrium and nonequilibrium algorithms for predicting small molecule porin permeation with potential of mean force methods

The goal of this project is to develop algorithms and open source tools for efficient equilibrium and nonequilibrium potential of mean force calculations for bacterial porins.

4/5/2018 – 4/5/2019

\$74,074 annual direct costs to the Chodera lab

Parker Institute for Cancer Immunotherapy Pilot Grant

Physics-based computational prediction of cancer-associated mutant MHC class II epitopes

The goal of this project is to develop algorithms and open source tools for efficient computation of MHC class II epitope binding affinities.

4/2/2018 – 4/1/2019

\$75,000 annual direct costs to the Chodera lab

NSF D3SC EAGER CTMC

A probabilistic framework for automated forcefield parameterization from experimental datasets

The goal of this project is to develop a scalable Bayesian inference infrastructure to parameterize molecular mechanics forcefields using experimental datasets.

9/1/2017 – 8/31/2019

\$52,030 annual direct costs to the Chodera lab

Silicon Therapeutics Sponsored Research Agreement

Development of efficient open source free energy based lead optimization algorithms

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

5/17/2017 – 11/17/2018

\$48,655 annual direct costs to the Chodera lab

Merck KGaA Sponsored Research Agreement

Developing automated workflows for absolute alchemical free energy calculations

The goal of this project is to develop open source automated workflows using absolute alchemical free energy calculations for use in prioritizing compounds for synthesis in drug discovery applications.

7/26/2016 – 1/25/2019

\$90,273 annual direct costs to the Chodera lab

Astra-Zeneca iMed Sponsored Research Agreement

Evaluating the potential for Markov state models of conformational dynamics to advance quantitative prediction of thermodynamics and kinetics of selective kinase inhibitors

The goal of this project is to evaluate the potential for Markov state models of conformational dynamics to quantitatively predict the thermodynamics and kinetics of selective kinase inhibitors to CK2 and SYK.

7/30/2015 – 1/30/2017

\$117,505 annual direct costs to the Chodera lab

Gerstner Family Foundation

Louis V. Gerstner, Jr. Young Investigator Award

Dates: 2/1/2013 – 1/30/2016

\$75,000 annual direct costs

MSKCC Functional Genomics Initiative (FGI) Rapid Response Grant

Biophysical characterization of clinically-identified kinase mutations

The goal of this project is to quantify the impact of clinically-identified kinase domain mutations on FDA-approved selective kinase inhibitor binding.

4/1/2016 – 3/31/2016
\$25,000 annual direct costs

MSKCC Functional Genomics Initiative (FGI) Rapid Response Grant
Biophysical characterization of clinically-identified K-Ras mutants
The goal of this project is to biophysically characterize clinically-identified K-Ras mutants.
7/1/2016 – 6/30/2016
\$25,000 annual direct costs

Fellowships

Marcus Wieder, Postdoctoral Research Fellow

Austrian Schrödinger Stipendium

10/1/2018 – 9/30/2019
Fellowship recipient direct paid

Simon Boothroyd, Postdoctoral Research Fellow

XtalPi / Open Force Field Consortium Distinguished Postdoctoral Fellowship

10/1/2018 – 9/30/2019
Fellowship recipient direct paid

Andrea Rizzi, CBM Graduate Student

MolSSI Open Force Field Predoctoral Fellowship

1/1/2019 – 6/30/2019
\$20,000/six months stipend support

Rafal P. Wiewiora, TPCB Graduate Student

DOD Peer-Reviewed Cancer Research Program Award

8/15/2017 – 8/14/2019
\$75,000/year for stipend and supplies

Karmen Čondić-Jurkić, Postdoctoral Research Fellow

Open Force Field Consortium Postdoctoral Fellowship

1/1/2019 – 6/30/2019
\$60,628 stipend and travel support

Chaya Stern, TPCB Graduate Student

MolSSI Phase II Fellowship

7/1/2018 – 12/31/2018
\$40,000/year stipend support

Chaya Stern, TPCB Graduate Student

MolSSI Phase I Fellowship

7/1/2018 – 12/31/2018
\$40,000/year stipend

Chaya Stern, TPCB Graduate Student

NSF Graduate Research Fellowship

8/1/2015 – 7/30/2018
\$32,000/year stipend support

Mehtap Isik, TPCB Graduate Student

Doris J. Hutchison Fellowship

7/1/2017 – 6/30/2018
\$38,668/year stipend support

Gregory A. Ross, Postdoctoral Fellow

Molecular Software Sciences Institute (MolSSI) Graduate Research Fellowship

\$50,000/year stipend support

Steven Albanese, GSK Graduate Student

Summer Internship, Schrödinger

Summer 2017

Ariën S. Rustenburg, PBSB Graduate Student

Summer Internship, Genentech

Summer 2015

Andrea Rizzi, CBM Graduate Student
Tri-I CBM Student Stipend Assistance
\$13,500/year stipend support

Collaborative Grants

2014 Functional Genomics Initiative (PI: James Hsieh, MSKCC)

Characterization of Cancer-derived mTOR Mutations for Precision Therapeutics

The goal of this project is to understand the mechanism underlying clinically-identified mTOR activating mutants and evaluate the potential for rapalog therapy to aid the 2% of cancer patients harboring mTOR mutations.

5/1/2015 – 4/30/2017

\$118,000

2014 STARR Cancer Consortium (PI: Minkui Luo, MSKCC)

Designing sinefungin scaffolds as specific protein methyltransferase inhibitors

The goal of this project is to use computational techniques that explicitly incorporate protein flexibility to design selective inhibitors for protein lysine methyltransferases.

1/1/2015 – 6/30/2017

\$125,000

Personnel

Current members

Postdocs

- Karmen Čondić-Jurkić, PhD Friedrich Alexander University, Erlangen (4/6/2019–)
Biomolecular force fields; open science; interoperability in molecular simulations
- Ana Silveira, PhD Federal University of Rio de Janeiro (8/1/2018–)
Integrative modeling of allosteric inhibition; modeling antimicrobial permeation of bacterial porins
- Jiaye Guo, PhD Stony Brook University (10/1/2018–)
Design of selective kinase inhibitors and emergence of resistance
- Simon Boothroyd, PhD Lancaster University (11/1/2018–)
Development of advanced biomolecular force fields for drug discovery
- William Glass, PhD Southampton (5/1/2020–)
Scalable alchemical free energy calculations for predicting the impact of resistance mutations in kinase inhibition
- Jaime Rodríguez-Guerra, PhD Autonomous University of Barcelona (4/1/2019–) (**Berlin group**)
Scalable machine learning and alchemical free energy calculations for drug discovery
- David Schaller, PhD Freie Universität Berlin (7/1/2020–) (**Berlin group**)
Scalable alchemical free energy calculations for drug discovery

Graduate Students

- Joshua Fass (9/1/2015–12/31/2019 *anticipated*)
Tri-Institutional Program in Computational Biology and Medicine (CBM)
Machine learning and statistical inference for biomolecular dynamics and forcefield parameterization
- Mehtap Isik (6/1/2015–9/30/2020 *anticipated*)
Tri-Institutional Program in Chemical Biology (TPCB)
Model experimental systems for protein-small molecule recognition; targeted nanoparticle design
- Ivy Zhang (8/1/2018–)
Program in Physiology, Biophysics, and Systems Biology (PBSB)
Scalable free energy calculations for predicting the impact of clinical mutations in antibodies and kinases
- Yuanqing Wang (7/1/2018–)
Program in Physiology, Biophysics, and Systems Biology (PBSB)
Machine learning of physical models for drug discovery
- Dominic Rufa (4/1/2019–)
Tri-Institutional Program in Computational Biology and Medicine (CBM)
Small molecule multi-objective design by free energy methods
- Alexander Payne (4/16/2020–)
Tri-Institutional Program in Chemical Biology (TPCB)
Conformational dynamics from cryo-EM data
- Talia Kimber (4/1/2019–) (**Berlin group**)
Charité Universitätmedizin (supervisor: Andrea Volkamer)
Freie Universität Berlin, Computer Science PhD program (supervisor: Frank Noé)
Machine learning for optimizing affinity/selectivity and predicting resistance

Technicians

- Erica Goldberger (7/1/2019–)
Automated human kinase expression and measurements of small molecule kinase inhibitor affinities to mutant kinases

Past trainees

Postdocs

- Hannah Bruce Macdonald, PhD University of Southampton (10/1/2018–9/30/2020)
Current position: *Scientist, Merck Research Laboratories, London*
- Marcus Wieder, PhD University of Vienna (9/1/2018–4/16/2020)
Current position: *Faculty, University of Vienna*
- Simon Boothroyd (until 10/31/2019)
Current position: *XtalPi Open Force Field Distinguished Postdoctoral Fellow* with **Michael Shirts** at the University of Colorado, Boulder
- Levi N. Naden (until 8/10/2018)
Current position: *Software Scientist* at the NSF **Molecular Sciences Software Institute (MoSSI)**
- Sonya M. Hanson (until 6/30/2017)
Next position: *Postdoctoral Researcher with Joachim Frank, Columbia University*
Current position: *Humboldt Research Fellow* with **Gerhard Hummer** at MPI Biophysics, Frankfurt
- Gregory Ross (until 6/30/2017)
Current position: *Senior Scientist, Free Energy Methods, Schrödinger*
- David W. H. Swenson (until 12/30/2015)
Current position: *Postdoctoral Researcher, Universiteit von Amsterdam*
- Daniel L. Parton (until 8/31/2015)
Current position: *Director, Data Science Practice, Bardess Group*
- Kyle A. Beauchamp (until 6/12/2015)
Current position: *Lead Data Scientist, Tempus*
- Jan-Hendrik Prinz (until 1/30/2015)
Current position: *Digital Solutions Architect, Keylight GmbH*
- Sarah E. Boyce (until 10/31/2013)
Current position: *Principal Scientist II, Drug Discovery Group, Schrödinger*

Graduate Students

- Rafal Wiewiora (6/1/2015–8/31/2020)
Tri-Institutional Training Program in Chemical Biology (TPCB)
Current position: *Redesign Science Distinguished Postdoctoral Fellow, Redesign Science*
- Ariën Sebastian Rustenburg (10/1/2013–10/19/2018)
Program in Physiology, Biophysics, and Systems Biology (PBSB)
- Andrea Rizzi (9/1/2015–12/31/2019)
Tri-Institutional Program in Computational Biology and Medicine (CBM)
Current position: *Postdoctoral Fellow, Michele Parrinello Group, ETH Zürich*
- Chaya Stern (4/01/2014–6/30/2020)
Tri-Institutional Training Program in Chemical Biology (TPCB)
Current position: *Computational Chemistry Scientist, DeepCure*
- Steven Albanese (6/1/2015–3/31/2019)
Gerstner Graduate Program (GSK)
Current position: *Senior Scientist, Drug Discovery Group, Schrödinger*
- Patrick B. Grinaway (7/1/2013–12/31/2018)
Program in Physiology, Biophysics, and Systems Biology (PBSB)
Current position: *Scientist, Onai*
- Julie M. Behr (1/10/2014–12/31/2016)
Tri-Institutional Program in Computational Biology and Medicine (CBM)
Current position: *Transferred to Imielinski lab after publishing three papers with the Chodera lab*

Technicians

- Binisha Karki (8/1/2019–8/28/2020)
Current position: *Research Associate, BionTech*

- Lucelenie Rodriguez (7/1/2015–12/31/2016; 12/4/2017–7/20/2018)
Current position: *Medical student*, [NYU School of Medicine](#)
- Erin Grundy (6/1/18–7/31/2019)
Current position: *Graduate student*, [George Washington University](#)