John D. Chodera

CONTACT

url	http://www.choderalab.org
email	john.chodera@choderalab.org
github	https://github.com/choderalab
ORCID iD	0000-0003-0542-119X
twitter	jchodera
mobile	646.737.3319
post	1275 York Ave, Box 357 New York, NY 10065

Education and positions

2012– **Assistant Member, Computational and Systems Biology Program, Sloan Kettering Institute**

2012– **Assistant Member, Memorial Sloan Kettering Cancer Center**

2013– **Assistant Professor, Physiology, Biophysics, and Systems Biology Program, Weill Cornell Graduate School of Medical Sciences**

2008–2012 **Independent Distinguished Postdoctoral Fellow, California Institute for Quantitative Biosciences (QB3), University of California, Berkeley**

2006–2008 **Postdoctoral researcher, Department of Chemistry, Stanford University**
With Vijay S. Pande (founder, Folding@Home distributed computing project)

1999–2006 **Ph.D. in Biophysics, University of California, San Francisco**
Dissertation: *Master equation models of macromolecular dynamics from atomistic simulation.*
Committee: Ken A. Dill (thesis advisor), Matthew P. Jacobson, Vijay S. Pande

1995–1999 **B.S. in Biology, California Institute of Technology**
Undergraduate research with Paul H. Patterson (experimental molecular neurobiology) and Jerry E. Solomon (computational chemistry)

Fellowships and awards

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

2005 Frank M. Goyan Award for outstanding work in physical chemistry, University of California, San Francisco

2000–2005 Howard Hughes Medical Institute Predoctoral Fellowship

Research overview

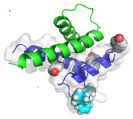
My research focuses on **redesigning the way we develop small molecules for chemical biology and drug discovery** and **bringing rigorous atomistic modeling into the high-throughput biology and genomics era**. By combining novel algorithmic advances to achieve orders-of-magnitude efficiency gains with powerful but inexpensive GPU hardware and distributed computing technologies, I am developing a new generation of tools for predicting small molecule binding affinities, designing small molecules with desired properties, quantifying drug sensitivity or resistance of clinical mutations, and understanding the detailed structural mechanisms underlying oncogenic mutations. As a core member of the Folding@home Consortium, my lab harnesses the computing power of hundreds of thousands of volunteers around the world to study functional implications of mutations and new opportunities for therapeutic design against cancer targets. Using a unique automated biophysical laboratory, we collect 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 methods and information theoretic principles for designing experiments and quantifying error.

Publications

Google Scholar statistics: http://goo.gl/qO0JW
MyNCBI Bibliography: http://goo.gl/e3kjgK
h-index: 34 / i10-index: 51 / citations: 6483 (31 Oct 2017)

* asterisk denotes equal contributions

Submitted and Under Review

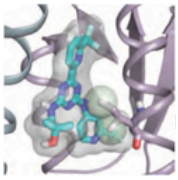


Wojnarowicz P, Desai B, Chin Y, Lima e Silva R, Ohnaka M, Lee SB, Cao MG, Ouerfelli O, Xu S, Goldgur Y, Miller M, Chaudhary J, Garland W, Stoller G, Albanese SA, Soni R, Philip J, Healey J, Vinagolu R, Norton L, Rosen N, Hendrickson R, Iavarone A, Dannenberg A, **Chodera JD**, Pavletich N, Lasorella A, Campochiaro P, Benezra R

A small-molecule pan Id antagonist, AGX51, shows strong anti-tumor and anti-neovascular activity

In revision for *Nature* ·

We identify the binding mode of a new small-molecule pan-Id antagonist prior to its confirmation by mass spectrometry crosslinking data.

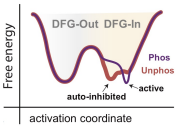


Andrew M. Intlekofer, Alan H. Shih, Bo Wang, Abbas Nazir, Ariën S. Rustenburg, Steven K. Albanese, Minal Patel, Christopher Famulare, Fabian M. Correa, Maria E. Arcila, Justin Taylor, Martin S. Tallman, Mikhail Roshal, Gregory A. Petsko, **Chodera JD**, Craig B. Thompson, Ross L. Levine, Eytan M. Stein

Acquired clinical resistance to IDH inhibition through *in trans* IDH2 mutations

In revision for *Nature* ·

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

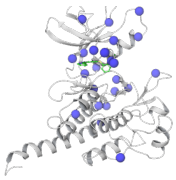


Emily F. Ruff, Joseph M. Muretta, Andrew Thompson, Eric Lake, Soreen Cyphers, Stephen K. Albanese, Sonya Hanson, Julie M. Behr, David D. Thomas, **Chodera JD**, Nicholas M. Levinson

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

Submitted to *Nature Communications* ·

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



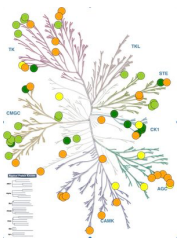
Kevin Hauser, Christopher Negron, Steven K. Albanese, Soumya Ray, Lingle Wang, Dmitry Lupyan, Thomas Steinbrecher, Robert Abel, and **Chodera JD**

Accurately predicting targeted kinase inhibitor resistance to clinical Abl mutations using alchemical free-energy calculations

Submitted to *Nature Communications* ·

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.

Preprints ahead of submission



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

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

Preprint ahead of submission · bioRχiv

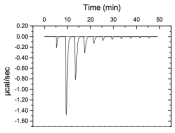
We engineer a library of human kinase domains with useful bacterial expression using a novel phosphatase coexpression technique.

Samuel Gill, Nathan M. Lim, Patrick Grinaway, Ariën S. Rustenburg, Josh Fass, Gregory Ross, **Chodera JD**, and David L. Mobley

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

Preprint ahead of submission · chemRxiv

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

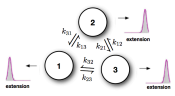


Boyce SE, Tellinghuisen JT, and **Chodera JD**

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

Preprint ahead of submission · bioRχiv

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.

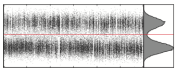


Chodera JD, Noé F, Hinrichs NS, Keller B, Elms PJ, Kaiser CM, Ewall-Wice A, Marqusee S, and Bustamante C

Bayesian hidden Markov model analysis of single-molecule biophysical experiments

Preprint ahead of submission · arχiv

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].



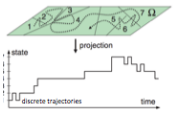
Chodera JD, Elms PJ, Swope WC, Prinz J-H, Marqusee S, Bustamante C, Noé F, and Pande VS

A robust approach to estimating rates from time-correlation functions

Preprint ahead of submission · arχiv

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

Reviews and Commentaries

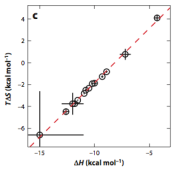


Chodera JD and Noé F

Markov state models of biomolecular conformational dynamics

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

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

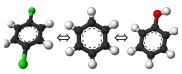


Chodera JD and Mobley DL

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

Annual Reviews in Biophysics 42:121, 2013 · DOI

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

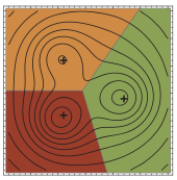


Chodera JD, Mobley DL, Shirts MR, Dixon RW, Branson KM, and Pande VS

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

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

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

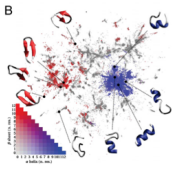


Prinz JH, Wu H, Sarich M, Keller B, Fischbach M, Held M, **Chodera JD**, Schütte, and Noé F

Markov models of molecular kinetics: Generation and validation

Journal of Chemical Physics 134:174105, 2011 · DOI

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

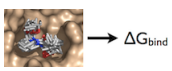


Chodera JD and Pande VS

The Social Network (of protein conformations)

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

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

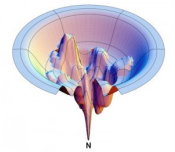


Shirts MR, Mobley DL, **Chodera JD**

Alchemical free energy calculations: Ready for prime time?

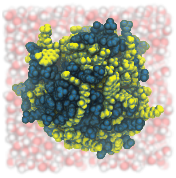
Annual Reports in Computational Chemistry 3:41, 2007 · DOI

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



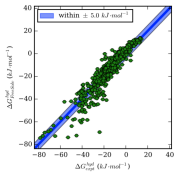
Dill KA, Ozkan SB, Weikl TR, **Chodera JD**, and Voelz VA
The protein folding problem: When will it be solved?
Current Opinion in Structural Biology 17(3):342, 2007 · DOI
A review of the current state of the protein folding problem.

Published and In Press



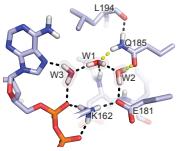
Shamay Y, Shah J, Tschaharganeh DF, Roxbury D, Budhathoki-Uprety J, Ijsik M, Mizrachi A, Nawaly K, Sugarman JL, Baut E, Neiman MR, Johnson DC, Sridharan R, Chu KL, Rajasekhar VK, **Chodera JD**, Lowe SW, and Heller DA
Quantitative self-assembly prediction yields targeted nanoparticles
Nature Materials, in press ·
A decision tree based on predicted physical properties and 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.

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
PLoS Computational Biology 13:e1005659, 2017 · DOI
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.



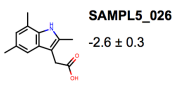
Matos GDR and Kyu DY and Loeffler HH and **Chodera JD** and Shirts MR and Mobley DL
Approaches for calculating solvation free energies and enthalpies demonstrated with an update of the FreeSolv database
Journal of Chemical & Engineering Data 62:1559, 2017 · DOI
We review alchemical approaches to computing solvation free energies and update FreeSolv—the most popular database of hydration free energies of neutral molecules—with more computed and experimental properties.

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
Nature Chemical Biology 13:494, 2017 · DOI
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.

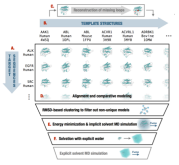


Cyphers S, Ruff E, Behr JM, **Chodera JD**, and Levinson NM
A conserved water-mediated hydrogen bond network governs allosteric activation in Aurora kinase A
Nature Chemical Biology 13:402, 2017 · DOI
Over 50 microseconds of aggregate simulation data on Folding@home reveal a surprisingly stable hydrogen bond network underlies allosteric activation by Tpx2.

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
Journal of Clinical Investigation 126:3529, 2016 · DOI
We use massively parallel distributed molecular simulations on Foldinghome to probe the mechanism activating mutations of the mTOR kinase identified in clinical populations.



Rusteburg AS, Dancer J, Lin B, Ortwine D, Mobley DL, and **Chodera JD**
Measuring cyclohexane-water distribution coefficients for the SAMPL5 challenge
Journal of Computer Aided Molecular Design, 30:945, 2016 · DOI
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.

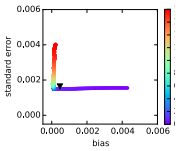


Parton DL, Grinaway PB, Hanson SM, Beauchamp KA, and **Chodera JD**

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

PLoS Computational Biology 12:e1004728, 2016 · DOI

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.

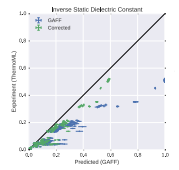


Chodera JD

A simple method for automated equilibration detection in molecular simulations

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

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

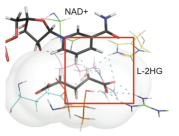


Beauchamp KA, Behr JM, Rustenburg AS, Bayly CI, Kroenlein K, and **Chodera JD**.

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

Journal of Physical Chemistry B 199:12912, 2015 · DOI

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 ThemoML Archive, which stores physical property data in an IUPAC-standard XML format, can eliminate these roadblocks and reveal issues with current generation forcefields.

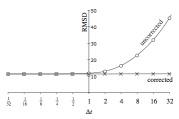


Intlekofer AM, Dematteo RG, Venetti S, Finley LWS, Lu Chao, Judkins AR, Rutenburg AS, Grinaway PB, **Chodera JD**, Cross JR, and Thompson CB

Hypoxia introduces production of L-2-Hydroxyglutarate

Cell Metabolism 22:1–8, 2015 · DOI

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

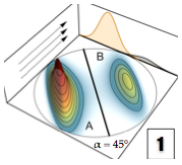


Sivak DA, **Chodera JD**, and Crooks GE

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

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

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

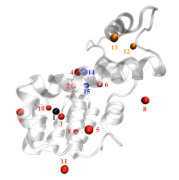


Prinz J-H, **Chodera JD**, and Noé F

Spectral rate theory for two-state kinetics

Physical Review X 4:011020, 2014 · DOI

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.

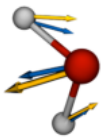


Wang K, **Chodera JD**, Yang Y, and Shirts MR

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

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

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.

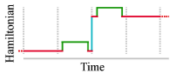


Wang L-P, Head-Gordon TL, Ponder JW, Ren P, **Chodera JD**, Eastman PK, Martinez TJ, and Pande VS

Systematic improvement of a classical molecular model of water

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

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.



Sivak DA, **Chodera JD**, and Crooks GE

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

Physical Review X 3:011007, 2013 · DOI

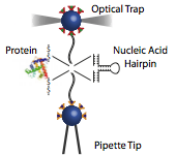
All molecular dynamics simulations introduce error into the sampled distribution by virtue of the finite timestep used to integrate the equations of motion on a digital computer. While traditional approaches to analyzing this error are extremely complicated, we show how interpreting finite-timestep integrators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

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

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

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.

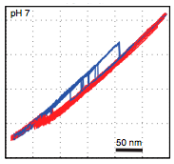


Elms PJ, **Chodera JD**, Bustamante CJ, Marqusee S

The limitations of constant-force-feedback experiments

Biophysical Journal 103:1490, 2012 · DOI

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.

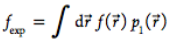


Elms PJ, **Chodera JD**, Bustamante C, Marqusee S

The molten globule state is unusually deformable under mechanical force

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

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.

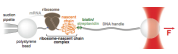


Pitera JW and **Chodera JD**

On the use of experimental observations to bias simulated ensembles

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

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.

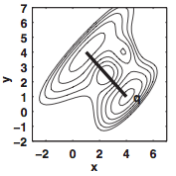


Kaiser CM, Goldman DH, **Chodera JD**, Tinoco I, Jr., and Bustamante C

The ribosome modulates nascent protein folding

Science 334:1723, 2011 · DOI

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

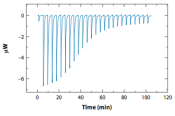


Chodera JD and Pande VS

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

Physical Review Letters 107:098102, 2011 · DOI

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

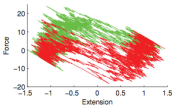


Tellinghuisen JT and **Chodera JD**

Systematic errors in isothermal titration calorimetry: Concentrations and baselines

Analytical Biochemistry 414:297, 2011 · DOI

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

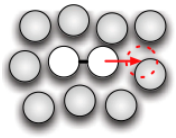


Minh DDL, **Chodera JD**

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

Journal of Chemical Physics 134:024111, 2011 · DOI

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.

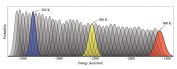


Nilmeier JP, Crooks GE, Minh DDL, and **Chodera JD**

Nonequilibrium candidate Monte Carlo is an efficient tool for equilibrium simulation

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

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.

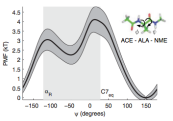


Prinz J-H, **Chodera JD**, Pande VS, Smith JC, and Noé F

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

Journal of Chemical Physics 134:244108, 2011 · DOI

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

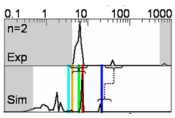


Chodera JD, Swope WC, Noé F, Prinz J-H, Shirts MR, and Pande VS

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

Journal of Chemical Physics 134:244107, 2011 · DOI

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

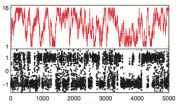


Noé F, Doose S, Daidone I, Löllmann M, Sauer M, **Chodera JD**, and Smith JC

Dynamical fingerprints: A theoretical framework for understanding biomolecular processes by combination of simulation and kinetic experiments

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

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.

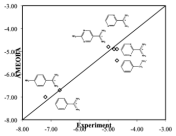


Chodera JD and Shirts MR

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

Journal of Chemical Physics 135:194110, 2011 · DOI

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.

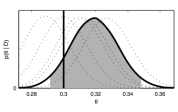


Ponder JW, Wu C, Ren P, Pande VS, **Chodera JD**, Mobley DL, Schnieders MJ, Haque I, Lambrecht DS, DiStasio RA Jr., Head-Gordon M, Clark GNI, Johnson ME, and Head-Gordon T

Current status of the AMOEBA polarizable force field

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

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



Chodera JD and Noé F

Probability distributions of molecular observables computed from Markov models. II. Uncertainties in observables and their time-evolution

Journal of Chemical Physics 133:105102, 2010 · DOI

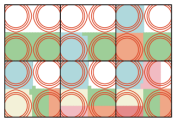
A simple Bayesian approach for the modeling of statistical uncertainties in kinetic and equilibrium quantities computed from Markov state models of biomolecular dynamics.

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

Biophysical Journal 98:3062, 2010 · DOI

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.

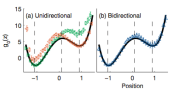


Bacallado S, **Chodera JD**, and Pande VS

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

Journal of Chemical Physics 131:045106, 2009 · DOI

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.

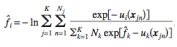


Minh DDL, **Chodera JD**

Optimal estimators and asymptotic variances for nonequilibrium path-ensemble averages

Journal of Chemical Physics 131:134110, 2009 · DOI

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.

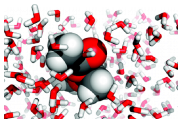


Shirts MR, **Chodera JD**

Statistically optimal analysis of samples from multiple equilibrium states

Journal of Chemical Physics 129:124105, 2008 · DOI

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.



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

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

Journal of Medicinal Chemistry 51:769, 2008 · DOI

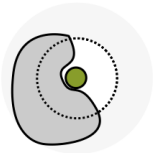
A blind evaluation of the accuracy of alchemical free energy methods for computing gas-to-water transfer free energies (solvation free energies) of small molecules demonstrates that modern forcefields are likely sufficiently accurate to be useful in drug design.

Mobley DL, Dill KA, and **Chodera JD**

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

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

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

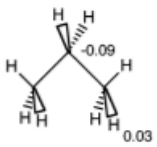


Shirts MR*, Mobley DL*, **Chodera JD**, and Pande VS

Accurate and efficient corrections for missing dispersion interactions in molecular simulations

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

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.

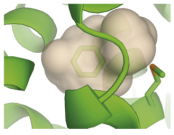


Mobley DL, Dumont E, **Chodera JD**, Bayly CI, Cooper MD, and Dill KA

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

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

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

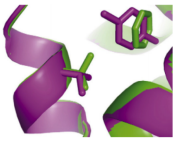


Mobley DL, Graves AP, **Chodera JD**, McReynolds AC, Shoichet BK, and Dill KA

Predicting absolute ligand binding free energies to a simple model site

Journal of Molecular Biology 371:1118, 2007 · DOI

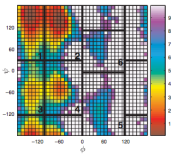
We show how alchemical free energy calculations are capable of accurate blind prediction of small-molecule binding affinities to a simple model protein binding site.



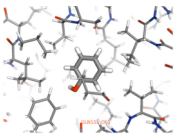
Mobley DL, **Chodera JD**, and Dill KA
Confine-and-release method: Obtaining correct binding free energies in the presence of protein conformational change
Journal of Chemical and Theoretical Computation 3:1231, 2007 · DOI
We present a general scheme for obtaining correct ligand binding affinities when protein conformational change is implicated in ligand binding.

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
Journal of Chemical Physics 126:155101, 2007 · DOI
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 the equilibrium populations of these states may too small for standard structural biology techniques to detect.

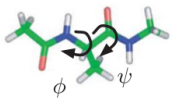
Ozkan SB, Wu GA, **Chodera JD**, and Dill KA
Protein Folding by Zipping and Assembly
Proceedings of the National Academy of Sciences 104:11987, 2007 · DOI
A review of the utility of the proposed zipping and assembly mechanism for the concomitant formation of secondary and tertiary structure in protein folding for predicting folding pathways and native structures.



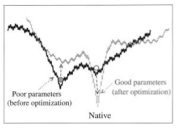
Chodera JD, W. C. Swope, J. W. Pitera, C. Seok, and K. A. Dill
Use of the weighted histogram analysis method for the analysis of simulated and parallel tempering simulations
Journal of Chemical Theory and Computation 3:26, 2007 · DOI
The weighted histogram analysis method (WHAM), a mainstay of molecular dynamics simulation analysis, is thoroughly explained and modernized for the analysis of simulated and parallel tempering simulation data.



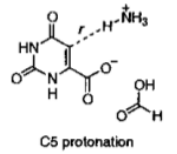
Mobley DL, **Chodera JD**, and Dill KA
On the use of orientational restraints and symmetry corrections in alchemical free energy calculations
Journal of Chemical Physics 125:084902, 2006 · DOI
We illustrate how orientational restraints can be used to greatly reduce the computational effort in alchemical calculations of ligand binding free energies, and clarify how symmetry corrections are necessary when molecules contain symmetric or pseudosymmetric substituents.



Chodera JD, Swope WC, Pitera JW, and Dill KA
Long-time protein folding dynamics from short-time molecular dynamics simulations
Multiscale Modeling and Simulation 5:1214, 2006 · DOI
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.



Seok C, Rosen JB, **Chodera JD**, Dill KA
MOPED: Method for optimizing physical energy parameters using decoys
Journal of Computational Chemistry 24:89, 2003 · DOI
We propose a new way to optimize parameters for a physical energy function using decoy structures for protein folding studies.



Lee TS*, Chong LT*, **Chodera JD**, and Kollman PA
An alternative explanation for the catalytic proficiency of orotidine 5'-phosphate decarboxylase
Journal of the American Chemical Society 123:12837, 2001 · DOI
A combined QM and MD analysis of potential plausible mechanisms to explain the enormous catalytic acceleration of one of the most proficient enzymes known.

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2013– Schrödinger, LLC

Conferences organized

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Jan 2017
[smml:2017] Statistical Mechanics // Machine Learning
University of California, Berkeley, CA

Boston
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
Sep 2015
World Molecular Kinetics Workshop 2015
Freie Universität Berlin, Germany

Boston
May 2014
Free Energy Methods in Drug Design Workshop
Vertex Pharmaceuticals, Boston, MA

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Sep 2013
World Molecular Kinetics Workshop 2013
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Freie Universität Berlin, Germany

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Freie Universität Berlin, Germany

Peer reviewer for scientific journals

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Biopolymers
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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
Journal of the American Chemical Society
Molecular Physics
Nature Physics
Nature Communications
Pacific Symposium in Biocomputing
PLoS Computational Biology
PLoS One
Proceedings of the National Academy of Sciences
Structure

Funding

ACTIVE

Federal

NIH R01 GM121505-01
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 selective kinase inhibition.
09/15/2017 – 09/14/2022
$1,686,765 total costs

NSF D3SC EAGER CTMC (PI: Michael R. Shirts, University of Colorado, Boulder)
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.
09/01/2017 – 08/31/2019
$179,907 total costs

Industry

Merck KGaA Collaboration
Developing automated workflows for absolute alchemical free energy calculations
The goal of this project is to develop automated workflows for absolute alchemical free energy calculations with an open source code developed in the lab.
1 Aug 2016 – 31 Jul 2018
$387,176 total costs

Silicon Therapeutics Collaboration
Development of efficient open source free energy based lead optimization algorithms
The goal of this project is to develop scalable parallel workflows for lead optimization using alchemical free energy calculations with an open source code developed in the lab.
15 May 2017 – 14 May 2018
$84,076 total costs

Completed

Gerstner Family Foundation
Louis V. Gerstner, Jr. Young Investigator Award
Dates: 02/01/2013 – 01/30/2016
$225,000

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

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

Astra-Zeneca iMed Collaboration
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
$176,258

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.
05/01/2015 – 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.
01/01/2015 – 06/30/2017
$125,000

Pending applications

NIH 1R01GM124270-01A1 (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.
04/01/2018 – 03/31/2023
$504,494

NIH 1R01GM124150-01A1 (PI: Nicholas Levinson, UMN)
Unraveling multifaceted allosteric regulation in Aurora kinase through coupled experiment and theory
The goal of this project is to understand the mechanism of complementary mechanisms of Aurora activation
12/01/2017 – 11/30/2022
$466,303

NIH 1R01CA222843-01 (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.
09/01/2017 – 08/31/2022
$408,993

NIH 1R01GM123183-01A1
Protonation state effects in selective kinase inhibitor recognition
The goal of this project is to characterize the role of protonation state effects in selective kinase inhibitor recognition and explore ramifications for selective inhibitor design.
co-Is: Markus Seeliger (Stony Brook); Marilyn Gunner (CCNY)
07/01/2017 – 06/30/2022
$736,289

Past trainees

Postdocs

- Sonya M. Hanson (until 06/30/2017)
  Current position: *Postdoctoral Researcher*, **Stony Brook University**
- Gregory Ross (until 06/30/2017)
  Current position: *Scientist*, **Schrödinger**
- David W. H. Swenson (until 12/30/2015)
  Current position: *Postdoctoral Researcher*, **Universiteit von Amsterdam**
- Daniel L. Parton (until 08/31/2015)
  Current position: *Lead Data Scientist*, **Bardess Group**
- Kyle A. Beauchamp (until 06/12/2015)
  Current position: *Computational Research Scientist*, **Counsyl**
- Jan-Hendrik Prinz (until 01/30/2015)
  Current position: *Digital Solution Architect*, **Keylight GmbH**
- Sarah E. Boyce (until 10/31/2013)
  Current position: *Senior Scientist, Drug Discovery Group*, **Schrödinger**

References

- Vijay S. Pande (Stanford University // a16z)
  email: pande@stanford.edu
  url: http://pande.stanford.edu
- Ken A. Dill (Director, Laufer Center, Stony Brook University)
  email: dill@laufercenter.org
  url: http://dillgroup.stonybrook.edu
- Chris Sander (Director, cBio Center, Dana-Farber Cancer Institute)
  email: chris@sanderlab.org
  url: http://sanderlab.org
- Matthew P. Jacobson (UCSF)
  email: matt.jacobson@ucsf.edu
  url: https://jacobsonlab.wordpress.com/
- Benoît Roux (University of Chicago // Argonne National Laboratory)
  email: roux@uchicago.edu
  url: http://thallium.bsd.uchicago.edu/RouxLab/
- Gunnar Rätsch (Head, Biomedical Informatics Group, ETH Zürich)
  email: raetsch@inf.ethz.ch
  url: http://ratschlab.org