MMCC Results

MOLECULAR MODELING & COMPUTATIONAL CHEMISTRY

Vol. 14, No. 8 1 October 2005

Coverage period: 1 September 2005 through 30 September 2005
About 92 papers from 14 journals are cited.

Editorial and News

The December issue of *J. Comp. Chem.* is dedicated to reviewing the progress in biomolecular modeling programs. In his Editorial, Charles Brooks states that he solicited progress reports from major developers for Amber, BOSS/MCPRO, GROMOS, GROMACS, IMPACT, and NAMD. The issue is covered in the Journal Reviews section. Take care to browse through our report in that section; the articles are not covered in the main section because of their review nature.

After eight years, I am planning to step down as editor after this volume. As of yet, no replacement is apparent. I'll keep you posted in the editorials for the last two issues of this volume, nos. 9 & 10.

David D. Busath, Editor

1. APPLICATIONS

1.1. *Small Molecules*

General and Model Systems

!

Potentials of mean force for the interaction of blocked alanine dipeptide molecules in water and gas phase from MD simulations.

V.M. Dadarlat* [Purdue U]

Biophys. J. **89,** 1433-1445 [2005]

The 2D PMF and interaction profile for a pair of alanine dipeptide molecules in explicit water cannot be captured in a 1D PMF, with forces being twice as strong in some spots. Likewise, implicit salvation is inadequate. "A preference for helical conformations is observed at close encounter between molecules."

Shear viscosity and thermal conductivity of quadrupolar real fluids from molecular simulation.

G.A. Fernández* [U Stuttgart], J. Vrabec, and H. Hasse

Mol. Sim. **31**, 787-793 (2005)

Equilibrium MD was used with the Green-Kubo formalism to simultaneously calculate shear viscosity and thermal conductivity of F_2, N_2, O_2, CO_2, C_2H_6, C_2H_4, C_2F_6, C_3H_4, C_3H_6 and SF_6. The molecules were described by a two-center Lennard-Jones plus point quadrupole pair potential, with parameters adjusted to vapor-liquid equilibria. At low temperature and high density state points, the Green-Kubo integral for shear viscosity shows slow convergence. A new approach is offered to work around this problem.

Density-functional theory and ab initio Hartree-Fock studies on the structural parameters and chemical activity of the free radicals generated by benzoquinone and hydroquinone.

Y. Song, J. Xie* [Jiangsu U], H. Shu, G. Zhao, X. Lv and H. Cai

Bioorg. Med. Chem. **13**, 5658-5667 (2005)

The calculated geometrical parameters, the predicted IR spectra, and the chemical activities of free radicals and transition states were compared with those of benzoquinone and hydroquinone. The reactive mechanisms of free radicals generated by benzoquinone and hydroquinone are also discussed using *ab* initio Hartree-Fock (HF) methods.

MMCC Results
David Busath, Ed.
706 Sunny Lane
Orem, UT 84058

Tel. (801) 422-8753
Fax (801) 422-0700
e-mail: *mmccresults@comcast.net*

David Busath, M.D., Professor, Dept. of Physiology and Dev. Biol. Brigham Young Univ., Provo, UT

Editor Emeritus: Bruce Gelin, Ph.D.
Dr. Gelin was founder of MMCC Results and edited volumes 1-6.

MMCC Results (ISSN 1061-6381) is published ten times per year at the beginning of each month except January and August by the independent business, MMCC Results. Mention of software, hardware, or other products is for informational purposes only and does not constitute an endorsement or recommendation by MMCC Results nor by the authors of the paper cited. All product names are the trademarks or registered symbols of their respective holders.
Marginal symbols indicate that the authors acknowledged the use of a software package from a commercial sourse. **A** refers to Accelrys Inc. and **T** to Tripos Inc. Other companies are denoted by their name in a box. Papers of special interest are marked by an exclamation point.

Copyright © 2005 MMCC Results

Associate Editor:
Thomas Cheatham
Univ. of Utah, Salt Lake City, UT

Assistant Editors:
Alan C. Cheng
Pfizer Global R&D, Cambridge, MA

Anton Feenstra
Vrije Univ., Amsterdam, Netherlands

R. Nageswara Ramireddy
Genomik Design Pharmaceuticals Pvt. Ltd. Hyderabad, India

Intrinsic relative stabilities of the neutral tautomers of arginine side-chain models.

J. Norberg* [Karolinaska Inst], N. Foloppe, and L. Nilsson

J. Chem. Theory and Comput. **1**, 986-993 (2005)

N-methyl-guanidine and *N*-ethyl-guanidine compounds were used to model the charged and all neutral protonation states of the arginine side chain. QM calculations are used to investigate the relative stabilities of all five neutral tautomers. The relative stabilities were obtained in vacuum, water and chloroform, by combining the QM calculations with a continuum solvation model. Significant differences in stability are found between the neutral tautomers, in both water and chloroform.

Water and Solvation

Structural properties of water: Comparison of the SPC, SPCE, TIP4P, and TIP5P models of water.

J. Zielkiewicz * [Gdańsk University of Technology]

J. Chem. Phys. **123,** 10450101-10450106 (2005)

Ordering of neighbors is all localized to the first and second shells, which are distinctly divided and have 43 J/mol-K and 12 J/mol-K respectively. The orientation is the only significant contributor to the entropy. Entropy and hydrogen bonding are closest to experimental for SPC and TIP4P models, which are recommended for biomolecular simulations.

Hydration properties and potentials of mean force of nonpolar amino acid residues in water: A pertubation theoretic approach.

D.G. Renzi, C.O. Stoico, and F. Vericat* [U Nac La Plata]

J. Chem. Phys. **123,** 10450201-10450210 (2005)

FEP simulations are used to estimate the solute-solvent interactions and the PMF for approximations of amino acids. Comparison with GROMOS shows that accuracy varies with residue species. Hydrophobicity is analyzed in terms of solute-water and solute-solute correlations.

Organic Solvents

Molecular dynamics simulation of fluorination effect for solvation of trifluoromethylbenzoic acid isomers in supercritical carbon dioxide.

H. Higashi* [Kanazawa U] , Y. Iwai , K. Miyazaki , and Y. Arai

Mol. Sim. **31**, 725-730 (2005)

MD simulation was applied to investigate the interactions between carbon dioxide and the solutes of carbon dioxide + trifluoromethylbenzoic acid isomer and carbon dioxide + methylbenzoic acid isomer systems. It was found that the interactions between carbon dioxide and trifluoromethyl group in trifluoromethylbenzoic acid isomers were stronger than those between carbon dioxide and the methyl group in methylbenzoic acid isomers.

Medicinal Chemistry and Drug Design

A Three-dimensional Model of the Human Immunodeficiency Virus Type 1 Integration Complex

J. Wielens* [Monash U], I.T. Crosby, and D.K. Chalmers

J Comput Aided Mol Des **19**, 301-317 (2005)

Analysis of a homology model of the HIV-1 integrase dimer, two viral DNA strands and one host DNA mimicking strand, based on the Tn5 transposase structure, identifies key residues and interacting regions, which are also highly conserved.

Theoretical and experimental design of atypical kinase inhibitors: Application to p38 MAP kinase.

K.F. McClure* [Pfizer], Y.A. Abramov* [Pfizer], E.R. Laird, J.T. Barberia, W. Cai, T.J. Carty, S.R. Cortina, D.E. Danley, A.J. Dipesa, K.M. Donahue, M.A. Dombroski, N.C. Elliott, C.A. Gabel, S. Han, T.R. Hynes, P.K. LeMotte, M.N. Mansour, E.S. Marr, M.A. Letavic, J. Pandit, D.B. Ripin, F.J. Sweeney, D. Tan, and Y. Tao

J. Med. Chem. **48**, 5728 - 5737 (2005)

Computational approaches including structure-based modeling and descriptor-based QSAR models are used to find replacement bioisosteres for the benzimidazolone core in a series of p38a inhibitors.

The first de novo-designed antagonists of the human NK2 receptor.

M.A. Ali, N. Bhogal, J.B.C. Findlay, and C.W.G. Fishwick* [U Leeds]

J. Med. Chem. **48**, 5655-5658

A new class of NK2 receptor antagonists is developed using a de novo molecular design program called SPROUT and a homology model of a GPCR.

Structure-based approaches to improve selectivity: CDK2-GSK3β binding site analysis.

A. Vulpetti* [Nerviano Med Sci], P. Crivori, A. Cameron, J. Bertrand, M.G. Brasca, R. D'Alessio, and P. Pevarello

J. Chem. Inf. Model. **45**, 1282-1290 (2005)

Comparison of CDK2 versus GSK3β binding sites using the GRID/CPCA and GRIND/CPCA methods suggests potential sites where optimization of a compound may provide selectivity between the two targets.

An automated system for the analysis of G protein-coupled receptor transmembrane binding pockets: Alignment, receptor-based pharmacophores, and their application.

N.A. Kratochwil* [Roche], P. Malherbe, L. Lindemann, M. Ebeling, M.C. Hoener, A. Mühlemann, R.H.P. Porter, M. Stahl, and P.R. Gerber

J. Chem. Inf. Model. **45**, 1324-1336 (2005)

Pharmacophore-like models derived from GPCR homology models are used for coarse assessments of selectivity issues, chemical design idea generation, and supporting mutagenesis studies.

Quantitative Structure-Activity Relations

QSAR study on thiazole and thiadiazole analogues as antagonists for the adenosine A_1 and A_3 receptors.

A. Borghini, D. Pietra, P. Domenichelli and A.M. Bianucci* [U Pisa]

Bioorg. Med. Chem. **13**, 5330-5337 (2005)

A QSAR study was carried out on thiazole and thiadiazole analogues as antagonists for adenosine A_1 and A_3 receptors. CODESSA software is used for application of datasets led to QSAR equations based on three and four descriptors for the adenosine A_1 and A_3 receptor ligands. The obtained models are useful to understand the main structural features that strongly correlate with the target property.

Exploration of a binding mode of indole amide analogues as potent histone deacetylase inhibitors and 3D-QSAR analyses.

Y. Guo, J. Xiao, Zongru Guo* [Chinese Acad Med Sci and Peking Med Coll], F. Chu, Y. Cheng and Song Wu

Bioorg. Med. Chem. **13**, 5424-5434 (2005)

Docking simulations and 3D-QSAR include CoMFA and CoMSIA analyses were used on a series of indole amide analogues as potent histone deacetylase inhibitors. 3D-QSAR and docking studies validated each other and provided insight into the structural requirements for activity of this class of molecules as HDAC inhibitors. The CoMFA and CoMSIA PLS contour maps and MOLCAD-generated active site electrostatic, lipophilicity, and hydrogen-bonding potential surface maps. Docking studies provided good insights into inhibitor-HDAC interactions at the molecular level.

A

A quantitative structure-activity relationship study on some series of anthranilic acid-based matrix metalloproteinase inhibitors.

S.P. Gupta* [Birla Inst of Tech & Sci] and S. Kumaran

Bioorg. Med. Chem. **13**, 5454 -5462 (2005)

A QSAR study was performed on four different series of anthranilic acid-based matrix metalloproteinase (MMP) inhibitors. The QSAR results indicated the sulfonamide group plays an important role in the inhibition activity of the inhibitors. The effectiveness of sulfonamide group is increased by the presence at the aryl rings or at the sulfonamide nitrogen itself of nitrogen-containing or some such substituents that can increase the electronic character of the sulfonamide group. The inhibition mechanism seems to predominantly involve the electronic interactions between the inhibitors and the enzymes.

Combinatorial design of nonsymmetrical cyclic urea inhibitors of aspartic protease of HIV-1.

V. Frecer, E. Burello and S. Miertus*
[Int Cent for Sci and High Tech]

Bioorg. Med. Chem. 13, 5492 -5501 (2005)

Computer-assisted combinatorial chemistry methods were used to design a small focused virtual library of nonsymmetrically substituted cyclic urea inhibitors of the aspartic protease (PR). A target-specific LUDI-type scoring function, parameterized for a QSAR training set of known cyclic urea inhibitors and validated on a set of compounds not included into the training set, is used to predict the inhibition constants (K_i) of the generated analogs toward the HIV-1 PR. ADME properties suggested the cyclic ureas are endowed with a wide range of favorable pharmacokinetic properties, favorable for the discovery of a potent orally administrable antiviral drug.

Quantitative Structure-Activity Relationships (cont'd)

A QSAR review on melanoma toxicity.

R.P. Verma, M.B. Suresh, A. Kurup and C. Hansch* [Pomona Coll]

Bioorg. Med. Chem. **13**, 5508-5526 (2005)

An attempt is made to collect the data for different sets of compounds and their toxicities toward melanoma cells by the formulation of a total number of 36 QSAR studies.

1-Substituted pyrazolo[1,5-*c*]quinazolines as novel Gly/NMDA receptor antagonists: Synthesis, biological evaluation, and molecular modeling study.

F. Varano* [U Stud Firenze], D. Catarzi, V. Colotta, F. Romana Calabri, O. Lenzi, G. Filacchioni, A. Galli, C. Costagli, F. Deflorian, and S. Moro

Bioorg. Med. Chem. **13**, 5536-5549 (2005)

A molecular modeling study was carried out to understand receptor affinity and selectivity of a new set of pyrazoloquinazoline derivatives of 5,6-dihydro-pyrazolo[1,5-*c*]quinazoline-2-carboxylates, bearing different substituents (COOEt, Cl, Br, CH_3, and COOH) at position-1.

Binding studies and GRIND/ALMOND-based 3D QSAR analysis of benzothiazine type K_{ATP}-channel openers.

E. Carosati, H. Lemoine, R. Spogli, D. Grittner, R. Mannhold, O. Tabarrini, S. Sabatini, and V. Cecchetti* [U Perugia]

Bioorg. Med. Chem. **13**, 5581-5591 (2005)

Binding studies were performed for seventeen 1,4-benzothiazine potassium channel openers in rat aromatic smooth muscle cells and cardiomyocytes and compared with published data and derived 3D-QSAR models using GRIND/ALMOND descriptors. 3D-QSAR results in PLS models of two latent variables for all three activities with determination coefficients of 0.97 (smooth muscle relaxation) and 0.94 (smooth muscle cells- and cardiomyocytes-binding). The carbonyl on the N-4 substituent, the hydrogen bond acceptor at C-6, the five-membered ring at N-4, and the *gem*-dimethyls mainly guide strong binding and strong smooth muscle relaxation.

Validation of a histamine H_3 receptor model through structure-activity relationships for classical H_3 antagonists.

S. Lorenzi, M. Mor* [U Stud Pharm], F. Bordi, S. Rivara, M. Rivara, G. Morini, S. Bertoni, V. Ballabeni, E. Barocelli, and P.V. Plazzi

Bioorg. Med. Chem. **13**, 5647-5657 (2005)

A 3D model of the rat histamine H3 receptor was built by comparative modeling from the crystallographic coordinates of bovine rhodopsin and its ability to predict the potency of known and new H3 antagonists were discussed. Molecular docking was used to identify a putative binding site for classical, imidazole-derived H3 antagonists.

1.2. *Biopolymers*

Protein Sequence Analysis and Alignment

BAliBASE 3.0: Latest developments of the multiple sequence alignment benchmark

J.D. Thompson* [CNRS], P. Koehl, R. Ripp, and O. Poch

Proteins **61**, 127-136 (2005)

The new release (3.0) of BAliBASE, including new and more complex test cases, like full-length sequences, to a new total of 6255 sequences, and an updated web-interface, is described.

Protein Structure Prediction

An atomic environment potential for use in protein structure prediction.

C.M. Summa, M. Levitt and W.F. DeGrado* [U Penn]

J. Mol. Biol. **352**, 986-1001 (2005)

A knowledge-based scoring function for recognizing native protein structures in a set of decoys resolves issues with pair-wise statistical potentials by instead capturing the microenvironment of each atom.

Comparative or Homology Modeling

Experimentally constrained topology models for 51,208 bacterial inner membrane proteins.

E. Granseth, D.O. Daley, M. Rapp, K. Melén and G. von Heijne* [Stockholm U]

J. Mol. Biol. **352**, 489-494 (2005)

Experimental topology information for 608 *E. coli* proteins is used to help predict the topology of sequence homologs. The resulting topology models cover ~30% of all predicted inner membrane proteins in 225 bacterial sequenced genomes.

Peptide Conformational Analysis

Elongation of Ordered Peptide Aggregate of an Amyloidogenic Hexapeptide NFGAIL Observed in Molecular Dynamics Simulations with Explicit Solvent.

C. Wu, H. Lei, and Y. Duan* [UC Davis]

J. Am. Chem. Soc. **127,** 13530-13537 (2005)

MD simulation in explicit solvent probe the beta-sheet elongation and aggregation process of an amyloidogenic hexapeptide, NFGAIL.

Free energy landscapes of two model peptides: α-helical and β-hairpin peptides explored with Brownian dynamics simulation.

T. Ando* [Tokyo Univ. of Sci.] and I. Yamato

Mol. Sim. **31**, 683-693 (2005)

Brownian dynamics (BD) simulations are used for the folding simulation of a 13-mer α-helical peptide and a 12-mer β-hairpin peptide, giving successful folding simulations. In this model, the driving energy contribution towards folding came from both electrostatic and van der Waals interactions for the α-helical peptide and from van der Waals interactions for the β-hairpin peptide. The results predicted the native structures from conformations sampled by BD simulation.

Protein Structure Analysis

Does secondary structure determine tertiary structure in proteins?

H. Gong and G.D. Rose* [JHU]

Proteins **61**, 338-343 (2005)

Protein classification based on backbone dihedrals, expressed in 60° 'mesostate' bins, compares well with most other commonly used classifications. Implications for structural alignment and structure comparison and prediction are discussed.

Cooperative effects in hydrogen-bonding of protein secondary structure elements: A systematic analysis of crystal data using Secbase

O. Koch, M. Bocola, and G. Klebe* [Philipps-U Marburg]

Proteins **61**, 310-317 (2005)

Analysis of 1500 <1.5Å structures from ReliBase reveals increasing α-helix length to correlate with slightly shorter H-bonds (~3.02-2.98Å), and shorter H-bonds for the middle pair of a 'chain' of H-bonds in parallel β-sheets (~2.89 vs. ~2.92Å). This is ascribed to cooperative polarization effects. For 3_{10} helices the trend for the length is opposite (~3.0-3.2Å), but the C=O···N angle shifts from ~120° to ~105°.

Alpha-alpha linking motifs and interhelical orientations

D.E. Engel and W.F. Degrado* [U Pennsylvania]

Proteins **61**, 325-337 (2005)

Conformation-dependent residue preferences of α-α links (cf. β-turns) are derived from 1983 linked α-helices in the 2166 structures in the 25% PDB select (April 2002).

Generation and Analysis of a Protein–Protein Interface Data Set With Similar Chemical and Spatial Patterns of Interactions

S. Mintz, A. Shulman-Peleg, H.J. Wolfson,
and R. Nussinov* [NCI Frederick]

Proteins **61**, 6–20 (2005)

From all ~24k interfaces in the PDB, after filtering out those without biological significance and similar structure, from the ~4.6k interfaces all ~5.6M putative combined interfaces with similar size are constructed and stored in a database. Correlations between interface and fold similarities, selected examples, and possibilities for interface prediction, are discussed.

Protein Folding

Structure and stability of a model three-helix-bundle protein on tailored surfaces

T.A.T. Knotts, N. Rathore,
and J.J. de Pablo* [U Wisconsin–Madison]

Proteins **61**, 385-397 (2005)

A three-helix-bundle fragment of *S. aureus* Protein A is studied in the Hoang and Cieplack 'Go-like' model with additional terms for surface- and pulling-forces. On a neutral surface, the protein unfolds, and on an attractive surface it is more sensitive to unfolding by external (*e.g.*, pulling or shear) forces.

Determinants of protein stability and folding: Comparative analysis of beta-lactoglobulins and liver basic fatty acid binding protein

L. Ragona, G. Colombo* [ICRM-CNR], M. Catalano,
and H. Molinari* [U Verona]

Proteins **61**, 366-376 (2005)

PCA of the matrix of intra-molecular non-bonded interaction energy terms reveals 'hot-spots' that are key to the native state stability, and are shown to correlate with experimental data on folding and conserved sidechain-sidechain interactions.

Protein Folding (cont'd)

Transition state contact orders correlate with protein folding rates.

E. Paci, K. Lindorff-Larsen, C.M. Dobson* [U Cambridge], M. Karplus* [Harvard U], and M. Vendruscolo* [U Cambridge]

J. Mol. Biol. **352**, 495-500 (2005)

MD simulations restrained by experimental ϕ value data shows that "despite the high levels of heterogeneity in the transition state ensemble, the large majority of contributing structures have native-like topologies and that the native state contact order captures this phenomenon".

Accelerating all-atom protein folding simulations through reduced dihedral barriers.

R.G. Endres* [Princeton U]

Mol. Sim. **31**, 773-777 (2005)

All-atom protein folding simulations can be accelerated through a reduction of the dihedral barriers of the force field as exemplified with two small proteins.

Protein Design and Engineering

Evolutionary protein stabilization in comparison with computational design.

M. Wunderlich, A. Martin, C.A. Staab and F.X. Schmid* [U Bayreuth]

J. Mol. Biol. **351**, 1160-1168 (2005)

A comparison of higher stability mutants of Gβ1 (β1 domain of the streptococcal protein G) derived from in vitro evolution and previously reported computational protein design work by Mayo et al.

Evolutionary information for specifying a protein fold.

M. Socolich, S.W. Lockless, W.P. Russ, H. Lee, K.H. Gardner and R. Ranganathan* [UT Southwestern]

Nature **437**, 512-518 (2005)

Artificial proteins designed based on only statistical residue co-evolution information from a multiple sequence alignment of WW domains is sufficient to generate sequences that fold into native-like WW domain structures. A letter in the same issue describes characterization of the artificial WW domains' functional activity.

!

Protein Hydration

Interfaces and the driving force of hydrophobic assembly.

D. Chandler* [UC Berkeley]

Nature **437**, 640-647 (2005)

Review on recent advances in understanding of the hydrophobic effect.

!

Protein Electrostatics and Titration

Interactions of macromolecules with salt ions: An electrostatic theory for the Hofmeister effect

H.X. Zhou* [Florida State U]

Proteins **61**, 69-78 (2005)

A carefully derived analytical theory of macromolecule-ion interactions couples salting-in ((re-)solvation at low salt) with strengthening of intra-molecular ionic interactions, and salting-out (desolvation at high salt) with repulsive interactions with image charges in the water cavity created by the macromolecule.

!

Protein Electrostatics and Titration (cont'd)

Coupling between conformation and proton binding in proteins

J.A. Vila, D.R. Ripoll, Y.A. Arnautova, Y.N. Vorobjev, and H.A. Scheraga* [Cornell U]

Proteins **61***,* 56-68 (2005)

An interesting comparison between four solvation/ protonation schemes (SAS, *Null* i.e. 'bulk' titration, MBE and PB) is presented. On test sets of up to 21 proteins, the MBE and PB methods are most successful in native-state identification. Implications for protein folding and forcefield development are discussed.

Protein Dynamics

Exploring global motions and correlations in the ribosome.

J. Trylska* [ICN Warsaw U], V. Tozzini, and J.A. McCammon

Biophys. J. **89,** 1455-1463 [2005]

With a course-grained model, 500-ns simulations show anticorrelation of the L7/L12 and L1 lateral stalk movements, widening of the tRNA cleft, rotation of the small subunit in correlation with L1 stalk movement, and small fluctuations of the 3' tRNA termini and anticodon nucleotides that align the substrates for the reaction.

Fast Peptidyl cis-trans Isomerization within the Flexible Gly-Rich Flaps of HIV-1 Protease.

D. Hamelberg* [UCSD], and J. A. McCammon

J. Am. Chem. Soc. **127,** 13778-13779 (2005)

An accelerated MD approach based on Voter's hperdynamics scheme is applied to understand flap motion in solvated HIV-1 protease.

Structural and Dynamical Basis of Broad Substrate Specificity, Catalytic Mechanism, and Inhibition of Cytochrome P450 3A4.

H. Park* [Seoul Natl U], S. Lee* [Seoul Natl U], and J. Suh

J. Am. Chem. Soc. **127,** 13634-13642 (2005)

MD simulations and Autodock, applying the Cornell et al force field with new heme-thiolate parameters, investigate the dynamics of cytochrome P450 3A4 with various bound substrates.

Protein flexibility and rigidity predicted from sequence

A. Schlessinger and B. Rost* [Columbia U]

Proteins **61***,* 115-126 (2005)

A method using a dual neural network, the sequence and PROF predicted secondary structure and accessibility, predicts flexibility of residues and correlates well with both B-factors and NMR order parameters. In selected examples, structurally (propeller tunnel), dynamically (switch) and functionally (catalytic site) important parts were identified.

Large amplitude conformational change in proteins explored with a plastic network model: Adenylate kinase.

P. Maragakis* [Harvard U] and M. Karplus* [Harvard U]

J. Mol. Biol. **352**, 807-822 (2005)

A method called the plastic network model appears to predict the conformational change pathway for adenylate kinase based on the starting and ending conformations. All of the 45 known structures for adenylate kinase are consistent with the predicted pathway.

Ligand Binding

Molecular dynamics simulations reveal multiple pathways of ligand dissociation from thyroid hormone receptors.

L. Martínez, M.T. Sonoda, P. Webb, J.D. Baxter, M.S. Skaf* [U Estadual Campinas], and I. Polikarpov* [U São Paulo]

Biophys. J. **89,** 2011-2023 [2005]

The escape of nuclear receptor ligands from the nuclear receptor ligand binding domain must involve extensive conformational changes in the binding protein because the ligand is buried deep in the protein and there is no obvious exit pathway. Three paths for thyroid hormone escape were identified using locally enhanced sampling MD, and are proposed to be specific to cell function.

In-silico Screening using Flexible Ligand Binding Pockets: A Molecular Dynamics-based Approach

D. Sivanesan, R.V. Rajnarayanan, J. Doherty, and N. Pattabiraman* [Georgetown U]

J Comput Aided Mol Des **19**, 213-228 (2005)

A systematic analysis of 3500 ligands docked with FlexX into 51 structures of the human estrogen receptor α derived from MD with Amber, and into the hERα X-ray structure, is presented. Seventeen residues in the binding pocket contribute most to ligand binding, and 32 compounds preferentially bind the MD structures, not the X-ray structure.

Synthesis of malarial plasmepsin inhibitors and prediction of binding modes by molecular dynamics simulations.

K. Ersmark, M. Nervall, E. Hamelink, L.K. Janka, J.C. Clemente, B.M. Dunn, M.J. Blackman, B. Samuelsson, J. Åqvist, and A. Hallberg* [Uppsala U]

J. Med. Chem. **48**, 6090-6106 (2005)

Molecular dynamics in conjunction with the LIE method appears to predict experimental K_i values for a series of inhibitors for malarial aspartic proteases Plm I and II.

A common pharmacophore for a diverse set of colchicine site inhibitors using a structure-based approach.

T.L. Nguyen* [NCI], C. McGrath, A.R. Hermone, J.C. Burnett, D.W. Zaharevitz, B.W. Day, P. Wipf, E. Hamel, and R. Gussio* [NCI]

J. Med. Chem. **48**, 6107-6116 (2005)

Docking of a set of known tubilin assembly inhibitors to the known tubilin crystal structure predicts inhibitor binding modes. A pharmacophore model is derived based on the dock models.

A

A systematic analysis of the effect of small-molecule binding on protein flexibility of the ligand-binding sites.

C-Y. Yang, R. Wang, and S. Wang [U Michigan]

J. Med. Chem. **48**, 5648-5650 (2005)

Comparison of the B-factors of 67 protein-ligand co-crystal structures and 37 corresponding apo-structures finds that in 75% of the cases at least some binding site atoms become more flexible. Of the total binding site atoms, 71% become less mobile, while 29% become more mobile as measured by the B-factors.

!

Design of a folding inhibitor of the HIV-1 protease.

G. Tiana* [Univ. di Milano] , R. A. Broglia , L. Sutto , and D. Provasi

Mol. Sim. **31**, 765-771 (2005)

A simplified protein model is used together with MC simulations, to assess the destabilizing effect of peptides displaying the same sequence as specific fragments of the protein which are essential for its stability. Model calculations showed that it is unlikely that the protein can escape the inhibitory peptide by point mutations.

Ligand Binding (cont'd)

Effects of peripheral substituents on dia-stereoselectivity of the fifth ligand-binding to chlorophylls, and nomenclature of the asymmetric axial coordination sites.

T. Oba* [Inst Mol Sci] and H. Tamiaki

Bioorg. Med. Chem. **13**, 5733-5739 (2005)

There are 42 Chl molecules whose fifth ligands were identified; 33 of 42 molecules bound the fifth ligand at the axial position where the $C13^2$-methoxycarbonyl group protrudes through crystallographic data on PS2 and LHC2 complexes**.** Computational studies revealed the energetic gap between the 'back' and its opposite 'face' complexes was inherent to (B) Chls and that the $C13^2$-methoxycarbonyl moiety contributed relatively greatly to the diastereomeric preference in the ligand binding.

Enzyme Catalysis

Electronic Structure of Compound I in Human Isoforms of Cytochrome P450 from QM/MM Modeling.

C. M. Bathelt, J. Zurek, A. J. Mulholland* [U Bristol], and J. N. Harvey* [U Bristol]

J. Am. Chem. Soc. **127,** 12900-12908 (2005)

QM/MM with B3LYP:CHARMM27 calculations are applied to the cytochrome P450 compound I intermediate that uses its oxygen atom to abstract hydrogen or to form C-C double bonds. The main change in spin density relates to the cysteinyl sulfur and relates to system setup (substate).

Conformational Substates Modulate Hydride Transfer in Dihydrofolate Reductase.

I. F. Thorpe, and C. L. I. Brooks* [Scripps]

J. Am. Chem. Soc. **127,** 12997-13006 (2005)

The importance of protein dynamics (or presence of long-lived substates in the energy landscape) are highlighted in this QM/MM study investigating the influence of different ligands on the hydride transfer reaction in DHFR. PMF calculations assuming a single free energy barrier are also discussed (and shown to be problematic).

How Enzyme Dynamics Helps Catalyze a Reaction in Atomic Detail: A Transition Path Sampling Study.

J. E. Basner, and S. D. Schwartz* [Albert Einstein]

J. Am. Chem. Soc. **127,** 13822-13831 (2005)

QM/MM (CHARMM27/AM1) simulations apply transition path sampling algorithms to probe the reaction catalyzed by lactate dehydrogenase.

Insight into Enzymatic C-F Bond Formation from QM and QM/MM Calculations.

H. M. Senn, D. O'Hagan, and W. Thiel* [Max-Planck Inst]

J. Am. Chem. Soc. **127,** 13643-13655 (2005)

DFT/CHARMM QM/MM calculations investigate the only native fluorination enzyme, fluorinase, which catalyzes the formation C-F bonds.

Association of Cytochrome P450 Enzymes is a Determining Factor in their Catalytic Activity

E. Hazai* [U Massachusetts], Z. Bikadi, M. Simonyi, and D. Kupfer

J Comput Aided Mol Des **19**, 271-285 (2005)

A multi-state kinetic model of P450 catalytic and reductase components homo- and heterooligomerization and ligand bound states is presented with a putative molecular basis, and is shown to explain series of published and new experimental kinetic data.

Enzyme Catalysis (cont'd)

A

Metabolic regio- and stereoselectivity of cytochrome P450 2D6 towards 3,4-methylenedioxy-n-alkylamphetamines: In silico predictions and experimental validation.

P.H.J. Keizers, C. de Graaf, F.J.J. de Kanter, C. Oostenbrink, K.A. Feenstra, J.N.M. Commandeur, and N.P.E. Vermeulen* [Vrije U]

J. Med. Chem. **48**, 6117-6127 (2005)

Docking of a series of compounds to cyp2D6 does not explain the experimental SAR. Performing molecular dynamics on the docking results however appears to predict the sites of metabolism as well as the effect of a Phe120Ala mutation.

Intrinsic carbon-carbon bond reactivity at the manganese center of oxalate decarboxylase from density functional theory.

C.H. Chang and N.G.J. Richards* [U Florida]

J. Chem. Theory and Comput. **1**, 994-1007 (2005)

DFT calculations are used upon a series of hypothetical OxDC active site model structures. These calculations indicated the intrinsic, gas-phase reactivity of the *Bacillus subtilis* oxalate *decarboxylase* active center is to *oxidize* oxalate. DFT results suggested the protein environment modulates the intrinsic metallocenter reactivity, presumably by affecting the electronic distribution at the manganese center during catalysis.

Protein-Protein Interactions

Free energy landscapes for amyloidogenic tetrapeptides dimerization.

A. Baumketner and J.-E. Shea* [U Calif Santa Barbara]

Biophys. J. **89,** 1493-1503 [2005]

Of KFFE, KVVE, KLLE, and KAAE, those with V or F form amyloid fibrils experimentally. Replica exchange MD. For KFFE, the dimer stabilization is enthalpic whereas for KVVE it is more entropic. Dimer structures are heterogeneous, but include antiparallel β-sheet structures found in fibrils.

Prediction of interface residues in protein-protein complexes by a consensus neural network method: Test against NMR data

H. Chen and H.X. Zhou* [Florida State U]

Proteins **61***,* 21-35 (2005)

An updated and improved version of PPISP, including new data and a consensus clustering over models of varying coverage and accuracy, called cons-PPISP, yields 64% accuracy at 39% coverage for predictions from unbound structures. Examples of successful predictions and comparisons with NMR interaction data are discussed.

Statistical analysis of predominantly transient protein-protein interfaces

S. Ansari and V. Helms* [Saarland U]

Proteins **61***,* 344-355 (2005)

From a set of 153 non-redundant structures of transient protein complexes, 170 interfaces were analyzed. Helices and strands are under-represented at interfaces, while backbone-sidechain and relatively tight sterical packing dominate. These transient interfaces are relatively hydrophilic, to ensure stable un-bound states.

Assessing protein co-evolution in the context of the tree of life assists in the prediction of the interactome.

F. Pazos* [Imperial College], J.A.G. Ranea, D. Juan and M.J.E. Sternberg

J. Mol. Biol. **352**, 1002-1015 (2005)

An approach to predicting protein–protein interactions involves looking at similarity of phylogenetic tree topologies and additionally taking into account the canonical tree of life to detect non-standard evolutionary events.

Membrane Proteins and Lipid-Peptide Interactions

Hydroxide and proton migration in aquaporins.

M. Ø. Jensen, U. Röthlisberger, and C. Rovira* [Parc Científic de Barcelona]

Biophys. J. **89,** 1744-1759 [2005]

In aquaporin, the channel charges form a quadrupole along the channel axis and the single-file of water molecules in the channel organize into an opposing quadrupole. Based on *ab initio* MD, hydroxide would migrate to the center once inside the channel, but would be kept out of the channel by the negative ends of the channel quadrupole. Protons in the channel would be expelled quickly by the water quadrupole. Both ions move by Grotthus transport, but protons at the cytoplamic end of the channel leave by diffusion of a two-water complex.

Protein-Nucleic Acid Interactions

Fidelity Discrimination in DNA Polymerase β: Differing Closing Profiles for a Mismatched (G:A) versus Matched (G:C) Base Pair.

R. Radhakrishnan, and T. Schlick* [NYU]

J. Am. Chem. Soc. **127,** 13245-13252 (2005)

A reaction network model, complemented by transition path sampling simulations and QM/MM calculations, is applied to understand the fidelity of DNA replication/ repair by polymerases. Different numbers and structures of transition states are noted for matched versus mismatched base pairs.

Protein-nucleic acid recognition: Statistical analysis of atomic interactions and influence of DNA structure

D. Lejeune, N. Delsaux, B. Charloteaux, A. Thomas, and R. Brasseur* [U Agro Gembloux]

Proteins **61**, 258-271 (2005)

A thorough statistical analysis of 139 protein-DNA and 49 protein-RNA complexes reveals the nature and frequency of ionic, H-bond and hydrophobic interactions with ribose, phosphate, base-edge. Preferences of amino-acid types and bases, dependence on DNA structure, and differences in protein-RNA and -DNA interactions and complexes are discussed.

Nucleic Acids

Dynamic Behavior of DNA Base Pairs Containing 8-Oxoguanine.

X. Cheng, C. Kelso, V. Hornak, C. delosSantos, A. P. Grollman, and C. Simmerling* [Stonybrook U]

J. Am. Chem. Soc. **127,** 13906-13918 (2005)

A variety of DNA duplexes with and without the damaged base 8-oxyguanine are studied in MD simulation in continuum (generalized Born) and explicit solvent. Enhanced sampling methods, including replica exchange, a modified "local" replica exchange, and locally enhanced sampling methods are applied.

Lipids and Surfactants

Areas of molecules in membranes consisting of mixtures.

O. Edholm* [Royal Inst Tech Sweden] and J.F. Nagle

Biophys. J. **89,** 1827-1832 [2005]

The partial-specific area formalism, based on analogy to the canonical partial-specific volume in physical chemistry, shows the condensing power of cholesterol (in DPPC), perhaps more clearly than other methods of dividing surface area.

Molecular Models of Lipopeptide Detergents: Large Coiled-Coils with Hydrocarbon Interiors.

E. Kelly, G. G. Prive, and D. P. Tieleman* [Calgary U]

J. Am. Chem. Soc. **127,** 13446-13447 (2005)

Models of aggregated alpha-helical coiled coil micelles with acyl chains attached to ornithine residues (in the center) are built with 12, 16, or 20 of the peptides and investigated in simulated annealing MD simulation.

Carbohydrates

Foldamer dynamics expressed via Markov state models. I. Explicit solvent molecular-dynamics simulations in acetonitrile, chloroform, methanol, and water.

Sidney P. Elmer, Sanghyun Park, and Vijay S. Pande* [Stanford U]

J. Chem. Phys. **123,** 11490201-11490214 (2005)

The folding of a polyphenylacetylene 12-mer in various organic solvents is analyzed from multiple short simulations using Markov models. Acetonitrile enhances, chloroform denatures, and water aggregates and traps the solute. Structures of the polymer are analyzed in a following article from the same group.

1.3. Polymers

Molecular dynamics simulations of polyampholytes inside a slit.

J. Feng* [East China U Sci Tech], H. Liu, Y. Hu

Mol. Sim. **31**, 731-738 (2005)

MD simulations are used, the slit has a strong effect on the properties of the polyampholyte. The effect is stronger when the electric field is weak, or the temperature is not too high. The width of the slit has only a little influence on the properties of solutions near the slit wall, values of several physical statistics are very close with different widths.

1.4. Surfaces, Catalysts, and Material Subjects

Comparison of model potentials for molecular-dynamics simulations of silica.

D. Herzbach, K. Binder, M.H. Müser* [U Western Ontario]

J. Chem. Phys. **123,** 12471101-12471110 (2005)

Three models for SiO_2, one with fixed charge, one with fluctuating charge, and one with polarizability, are compared. The fluctuating charge model needed corrections at the outset and still had large problems for transitions between various phases, whereas with the polarizability-based force field these issues were significantly resolved.

2. METHODOLOGY

Potentials and Parameters

A new set of molecular mechanics parameters for hydroxyproline and its use in molecular dynamics simulations of collagen-like peptides.

S. Park, R.J. Radmer, T.E. Klein* [Stanford U], V.S. Pande* [Stanford U]

J. Comp. Chem. **26,** 1612-1616 (2005)

A new set of parameters was developed that produces the correct ring pucker in hydroxyproline. Simulations with these parameters demonstrate that the collagen triple helix structure requires this correct ring pucker, and that hydroxylation of the prolines is important for this reason.

Force field validation for nucleic acid simulations: Comparing energies and dynamics of a DNA dodecamer.

S. Jha* [Univ Coll London], P.V. Coveney, and C.A. Laughton

J. Comp. Chem. **26,** 1617-1627 (2005)

Comparison of the AMBER98 force field as implemented in NAMD with that in Amber for ligand binding to a DNA dodecamer and other benchmarks show the NAMD accuracy to be adequate and that the advantages of NAMD for large scale simulations can be tapped with confidence.

New potential model for molecular dynamic simulation of liquid HF. I - Parameter optimization for charge equilibration method.

E. Bourasseau* [Commissariate al' Ene Atom], J.-B. Maillet, L. Mondelain, P.-M. Anglade

Mol. Sim. **31**, 705-713 (2005)

MD simulations of liquid HF is used to develop a new optimization method to obtain transferable parameters for charge equilibration method on the basis of ab initio reference data. The optimized parameters are able to reproduce the variations of the electrostatic potential calculated from an ab initio method in a liquid phase of HF molecules for different thermodynamic conditions. The proposed method is general, precise and efficient to obtain transferable and realistic parameters.

Energy Minimization

New general tools for constrained geometry optimizations.

L. De Vico, M. Olivucci and R. Lindh* [Cent Stu Sistemi Complessi]

J. Chem. Theory and Comput. **1**, 1029-1037 (2005)

A modified constrained geometry optimization method is designed and implemented. The changes include the choice of projection, quasi-line-search, and the use of a Rational Function optimization approach rather than a reduced-restricted-quasi-Newton-Raphson method in the optimization step. The results showed how geometrical constraints are implemented in an approach based on nonredundant curvilinear coordinates avoiding the inclusion of the constraints in the set of redundant coordinates used to define the internal coordinates.

Molecular Dynamics

Application of torsion angle molecular dynamics for efficient sampling of protein conformations.

J. Chen, W. Im, and C.L. Brooks III* [Scripps]

J. Comp. Chem. **26, 1565-1578 (2005)**

To get a more accurate internal coordinate force field, the "projection" approach of Katrich et al was extended using softened VDW and electrostatic interactions so that the flexibility inherent in bond lengths and angles was properly represented for the rigid bond lengths and angles used in torsion angle MD. Time steps can be lengthened, but are limited by some intrinsic complications.

Framework-based design of a new all-purpose molecular simulation application: The Adun simulator.

M.A. Johnston, I.F. Galván, and J. Villà-Freixa*
[Inst. Municipal d'Investigació Mèdica and U Pompeu Fabra]

J. Comp. Chem. **26,** 1647-1659 (2005)

Adun is a new programming framework that separates the program from underlying algorithms, providing "complete reusability." A package that can be adjusted to molecular simulations was developed and is here illustrated using QM/MM, FEP, and other standard MD projects.

Speed up of dynamic observables in coarse-grained molecular-dynamics simulations of unentangled polymers.

P.K. Depa and J.K. Maranas* [Penn State U]

J. Chem. Phys. **123,** 09490101-09490107 (2005)

Motions in course-grained models are faster than in atomistic counterparts by a predictable margin, in a way that relates to neighbor cage escapes.

Combined length scales in dissipative particle dynamics.

J. A. Backer* [U Amsterdam], C. P. Lowe, H.C.J. Hoefsloot, and P. D. Iedema

J. Chem. Phys. **123,** 11490501-11490510 (2005)

A method for combining dissipative (mesoscopic) dynamics with atomistic dynamics, with interconversions at the interface, is found to increase efficiency two fold in the system under consideration.

Multiscale coarse graining of liquid-state systems.

S. Izvekov and G.A. Voth* [U Utah]

J. Chem. Phys. **123,** 13410501-13410513 (2005)

In this approach to combining mesoscopic and atomistic simulations, forces are matched through use of a constraint for the instantaneous virial. It is illustrated with coarse-grained water and methanol molecules.

Peptide Conformational Analysis

Lattice models of peptide aggregation: Evaluation of conformational search algorithms.

M.T. Oakley, J.M. Garibaldi, and J.D. Hirst* [U Nottingham]

J. Comp. Chem. **26,** 1638-1646 (2005)

Fibril formation was probed using a Miyazawa-Jernigan force field and various MC algorithms on a series of small peptides. Replica exchange provided the most stable structures.

Structural Similarity Analysis

YAKUSA: A fast structural database scanning method

M. Carpentier* [U Paris], S. Brouillet, and J. Pothier

Proteins **61**, 137-151 (2005)

A fast method for (local) substructure similarity searches, based on Cα α/τ angles, is presented. The sensitivity and selectivity compare well to the best of other methods (like CE and DALI). Future application to rigorous/exhaustive structural classification is discussed.

Ligand Docking

A Flexible Docking Procedure for the Exploration of Peptide Binding Selectivity to Known Structures and Homology Models of PDZ Domains.

M. Y. Niv, and H. Weinstein* [Weill Med College]

J. Am. Chem. Soc. **127,** 14072-14079 (2005)

Simulated annealing MD (with a soft core potential) with rotamer search is developed into a methodology for a flexible peptide docking to homology models of PDF protein binding motifs.

General and targeted statistical potentials for protein-ligand interactions

W.T. Mooij* [Astex] and M.L. Verdonk

Proteins **61**, 272-287 (2005)

The development of a docking potential, and methodological aspects of the generation thereof, are presented. Potentials obtained perform on a level with e.g. GoldScore and ChemScore, but can be more directly linked and/or tailored to (additional) structural information and/or (specific) docking targets.

T

POEM: Parameter Optimization using Ensemble Methods: Application to target secific soring fnctions.

I. Antes* [Max-Planck Inst], C. Merkwirth, and T. Lengauer

J. Chem. Inf. Model. **45**, 1291-1302 (2005)

A new method and program, POEM, combines the DOE (Design Of Experiment) procedure with a variety of regression methods to target-specifically optimize scoring functions such as FlexX and Screenscore for structure-based docking.

Structure Determination

ABACUS, a direct method for protein NMR structure computation via assembly of fragments

A. Grishaev, C.A. Steren, B. Wu, A. Pineda-Lucena, C. Arrowsmith, and M. Llinás* [Carnegie Mellon U]

Proteins **61**, 36-43 (2005)

"A robust 'direct' approach for high-throughput bio-molecular structure determination via NMR" capable of handling ambiguous NOEs without a-priori assumptions, converges in ~15 cycles and is shown to reproduce a conventional NMR structure to within 1.2Å and 97% of NOESY assignments.

!

An assessment of the accuracy of methods for predicting hydrogen positions in protein structures

L.R. Forrest and B. Honig* [Columbia U]

Proteins **61**, 296-309 (2005)

The first and very thorough comparison of accuracy and efficiency of seven common modeling/simulation tools that add hydrogens to protein structures, with each other and with three X-ray and four neutron-diffraction structures with resolved hydrogens, is presented. Nearly all methods place NH's within the fluctuation radius, but for OH's differences are significant. The effects of different (if at all) treatment of ionization states are discussed.

3. J O U R N A L R E V I E W S

Journal of Computational Chemistry 26(1), January 15, 2005

1667 **Editorial.** C.L. Brooks III

1668-1688 **The Amber biomolecular simulation programs.** D.A. Case* [Scripps], T.E. Cheatham III, T. Darden, H. Gohlke, R. Luo, K.M. Merz Jr., A. Onufriev, C. Simmerling, B.Wang, and R.J. Woods

The program that developed in the late 1970's for "Assisted Model Building with Energy Refinement now contains a group of programs embodying a number of powerful tools of modern computational chemistry, focused on molecular dynamics and free energy calculations of proteins, nucleic acids, and carbohydrates."

1689-1700 **Molecular modeling of organic and biomolecular systems using BOSS and MCPRO.** W.L. Jorgensen* [Yale U] and J. Tirado-Rives

"An overview is provided of the capabilities for the current versions of the *BOSS* and *MCPRO* programs for molecular modeling of organic and biomolecular systems. Recent applications are noted, particularly for QM/MM studies of organic and enzymatic reactions and for protein-ligand binding."

1701-1718 **GROMACS: Fast, flexible, and free.** D. Van Der Spoel, E. Lindahl, B. Hess, G. Groenhof, A.E. Mark, and H. J.C. Berendsen* [U Groningen]

GROMACS is designed around parallel processingwith clusters of processors. It does not support an independent force field, but is compatible with GROMOS, OPLS, AMBER, and ENCAD. It has connections for QM/MM simulations and can handle polarizable shell models and flexible constraints.

1719-1751 **The GROMOS software for biomolecular simulation: GROMOS05.** M. Christen, P.H. Hünenberger, D. Bakowies, R. Baron, R. Bürgi, D.P. Geerke, T.N. Heinz, M.A. Kastenholz, V. Kräutler, C. Oostenbrink, C. Peter, D. Trzesniak, and W.F. van Gunsteren* [Swiss Fed Inst Tech Zürich]

GROMOS05 is the latest update replacing GROMOS96. It includes an analysis package, GROMOS++.

1752-1780 **Integrated Modeling Program, Applied Chemical Theory (IMPACT).** J.L. Banks, H.S. Beard, Y. Cao, A.E. Cho, W. Damm, R. Farid, A.K. Felts, T.A. Halgren, D.T. Mainz, J.R. Maple, R. Murphy, D.M. Philipp, M. P. Repasky, L.Y. Zhang, B.J. Berne, R.A. Friesner, E. Gallicchio, and R.M. Levy* [Rutgers U]

IMPACT includes both fixed and polarizable atom force fields, and is useful for biomolecular simulations involving organic medicinal compounds. "Explicit solvent simulations have been used to guide (the) design of implicit solvent models based on the generalized Born framework and a novel nonpolar estimator that have recently been incorporated into the program. With IMPACT it is possible to use several different advanced conformational sampling algorithms based on combining features of molecular dynamics and Monte Carlo simulations. The program includes two specialized molecular mechanics modules: Glide, a high-throughput docking program, and QSite, a mixed quantum mechanics/molecular mechanics module. These modules employ the IMPACT infrastructure as a starting point for the construction of the protein model and assignment of molecular mechanics parameters, but have then been developed to meet specialized objectives with respect to sampling and the energy function."

1781-1802 **Scalable molecular dynamics with NAMD.** J.C. Phillips, R. Braun, W. Wang, J. Gumbart, E. Tajkhorshid, E. Villa, C. Chipot, R.D. Skeel, L. Kalé, and K. Schulten* [U Illinois Champaign Urbana]

NAMD is freely distributed and is designed to scale for hundreds of processors on high-end parallel machines and for 10s of processors on low-end clusters. It uses the CHARMM and AMBER force fields. "This article, directed to novices as well as experts, first introduces concepts and methods used in the NAMD program, describing the classical molecular dynamics force field, equations of motion, and integration methods along with the efficient electrostatics evaluation algorithms employed and temperature and pressure controls used. Features for steering the simulation across barriers and for calculating both alchemical and conformational free energy differences are presented. The motivations for and a roadmap to the internal design of NAMD, implemented in C++ and based on Charm++ parallel objects, are outlined. The factors affecting the serial and parallel performance of a simulation are discussed. Finally, typical NAMD use is illustrated with representative applications to a small, a medium, and a large biomolecular system, highlighting particular features of NAMD, for example, the Tcl scripting language."

4. ADDRESSES OF PRINCIPAL AUTHORS

The production sites for the corresponding or principal authors are given in brackets in the citations. When not designated by the publisher, the first author is assumed to be the principal. Current addresses are listed here.

Yuri Abramov
yuriy.a.abramov@pfizer.com
Pfizer Global R&D
Eastern Point Rd
Groton, CT, 06340 USA

Iris Antes
antes@mpi-sb.mpg.de
Max-Planck-Institut für Informatik
Stuhlsatzenhausweg 85
D-66123 Saarbrücken, Germany

T. Ando
Dept. of Biol. Sci. & Tech.
Tokyo Univ. of Sci.
2641 Yamazaki, Noda-shi
Chiba, 278-8510, Japan

J. A. Backer
backer@science.uva.nl
Van 't Hoff Inst. for Mol. Sciences
University of Amsterdam
Nieuwe Achtergracht 166
1018 WV Amsterdam,
The Netherlands

Herman J. C. Berendsen
H.J.C.Berendsen@rug.nl
Groningen Biomolecular Sciences and Biotechnology Institute
University of Groningen
Nijenborgh 4
NL-9747 AG Groningen,
The Netherlands

A. Maria Bianucci
Dept. di Sci. Farma.
Univ. di Pisa
Via Bonanno 6
56126 Pisa, Italy

E. Bourasseau
Commissariat à l'Enegie Atomique
Dépt. de Phys. Théor. et Appl.
BP12, 91680
Bruyères-le-Châtel, France

Robert Brasseur
brasseur.r@fsagx.ac.be
Centre de Biophys. Moléc. Numér.
Fac. Univ. des Sci. Agronom.
Passage des Déportés 2
B-5030 Gembloux, Belgium.

Charles L. Brooks
brooks@scripps.edu
Department of Molecular Biology and Center for Theoretical Biological Physics
The Scripps Research Institute
10550 North Torrey Pines Road
La Jolla, CA 92037, USA

Mathilde Carpentier
mathilde@abi.snv.jussieu.fr
Atelier de BioInformatique
Université Paris 6
12 Rue Cuvier,
75005 Paris, France.

David A. Case
case@scripps.edu
Department of Molecular Biology
The Scripps Research Institute
10550 North Torrey Pines Rd,
TPC15
La Jolla, CA 92037, USA

David Chandler
chandler@cchem.berkeley.edu
Department of Chemistry
Univ. California, Berkeley
Berkeley, CA 94720, USA

Violetta Cecchetti
Lab. di Chem. e Chemioinf.
Dept. di Chim.
Univ. di Perugia
Via Elce di Sotto 10
I-06123 Perugia, Italy

Dr. Giorgio Colombo
g.colombo@icrm.cnr.it
ICRM-CNR
Via Mario Bianco 9, 20131
Milano, Italy.

Voichita M. Dadarlat
voichi@purdue.edu
Department of Chemistry
Purdue University
West Lafayette, IN 47907

William F. DeGrado
wdegrado@mail.med.upenn.edu
Dept. of Biochem. and Molec. Biophys. and Dept. of Chem.
Univ. of Pennsylvania
Philadelphia, PA 19104, USA

Christopher Dobson
cmd44@cam.ac.uk
Dept. Chemistry
Univ. Cambridge
Lensfield Rd.
Cambridge CB2 1EW, UK

Yong Duan
duan@ucdavis.edu
UC Davis Genome Center
Dept. of Applied Sci.
Univ. California
Davis, CA 95616, USA

Olle Edholm
oed@theophys.kth.se
Theoretical Biological Physics
Royal Institute of Technology
Stockholm, Sweden

R.G. Endres
Princeton Univ.
Princeton, NJ 08544-1014, USA

J. Feng
Dept. of Chem. and
State Key Lab. of Chem. Engg.
East China Univ. of Sci. & Tech.
Shanghai, 200237, P.R. China

G. A. Fernández
Inst. of Thermodynamics and Thermal Process Engg.
Univ. of Stuttgart
D-70550, Stuttgart, Germany

Colin Fishwick
colinf@chem.leeds.ac.uk
Dept. Chemistry
Univ. of Leeds
Leeds LS2 9JT, UK

Zongru Guo
Dept. of Med.Chem.
Inst. of Materia Medica
Chinese Acad. of Med. Sci. &
Peking Union Med.Coll.
Beijing 100050, China

S.P. Gupta
Dept. of Chem.
Birla Inst. of Tech. and Sci.
Pilani - 333031, India

Rick Gussio
gussio@ncifcrf.gov
Developmental Therapeutics
National Cancer Instit.
Frederick, MD 21702, USA

Anders Hallberg
Anders.Hallberg@orgfarm.uu.se
Dept. Medicinal Chem.
Uppsala University, BMC
Box 574
751 23 Uppsala, Sweden

Corwin Hansch
Dept. of Chem.
Pomona Coll.
Claremont, CA 91711, USA

Donald Hamelberg
dhamelbe@mccammon.ucsd.edu
HHMI and Dept. of Chem. and
Biochem.
Univ. California at San Diego
La Jolla, CA 92093, USA

Jeremy N. Harvey
jeremy.harvey@bris.ac.uk
Centre for Comp. Chem.
School of Chemistry
Univ. Bristol
Cantock's Close, Bristol BS8 1TS,
U. K.

Eszter Hazai
hazaie@chemres.hu
Sch. of Medicine, Dept. of Molec.
Pharmac. and Biochem.
Univ. of Massachusetts
Room 815, 364 Plantation St
Worcester, MA, 01605, USA
and
Inst. of Biomolec. Chem.
Chemical Research Center
POB 17, H-1525
Budapest, Hungary.

Gunnar von Heijne
gunnar@dbb.su.se
Dept. Biochemistry and Biophysics
Stockholm Univ.
SE-106 91 Stockholm, Sweden

Volkhard Helms
volkhard.helms@
bioinformatik.uni-saarland.de
Center for Bioinformatics
Saarland Univ.
P.O. 151150, D-66041,
Saarbrücken, Germany.

H. Higashi
Div. of Material Engg.
Grad. Sch. of Natural Sci. & Tech.
Kanazawa Univ.
Kakuma-machi
Kanazawa, 920-1192, Japan

Jonathan D. Hirst
jonathan.hirst@nottingham.ac.uk
School of Chemistry
University of Nottingham
University Park
Nottingham NG7 2RD, UK

Barry Honig
bh6@columbia.edu
Dept. Biochem. & Molec. Biophys.
Columbia Univ.
630 West 168th Street, BB2-221
New York, NY 10032, USA.

Shantenu Jha
s.jha@ucl.ac.uk
Centre for Computational Science
University College London
20 Gordon Street
London WC1H 0AJ, UK

William L. Jorgensen
William.Jorgensen@yale.edu
Department of Chemistry
Yale University
New Haven, CT 06520-8107, USA

Martin Karplus
marci@tammy.harvard.edu
Dept. Chem. and Chemical Biol.
Harvard Univ.
12 Oxford St.
Cambridge, MA 02138, USA

Gerhard Klebe
klebe@mailer.uni-marburg.de
Inst. für Pharmaz. Chem.
Philipps-Universität Marburg
Marbacher Weg 6
D-35032 Marburg, Germany

Teri E. Klein
teri.klein@stanford.edu
Department of Genetics
School of Medicine
Stanford University
Stanford, CA 94305, USA

Nicole Kratochwil
nicole_a.kratochwil@roche.com
Pharmaceuticals Division
F. Hoffmann-La Roche Ltd
CH-4070 Basel, Switzerland

Sangyoub Lee
sangyoub@snu.ac.kr
Dept. of Chem.
Seoul Natl. Univ.
Seoul 151-747, South Korea

Ronald M. Levy
ronlevy@lutece.rutgers.edu
Department of Chemistry and
Chemical Biology and BioMaPS
Institute for Quantitative Biology
Rutgers University
Piscataway, NJ 08854, USA

Roland Lindh
Cent. per lo Studio dei
Sistemi Complessi
Via Tommaso Pendola 37
I-53100 Siena, Italy

Miguel Llinás
llinas@andrew.cmu.edu
Dept. of Chem.
Carnegie Mellon Univ.
Pittsburgh, PA 15213, USA

A. Mallik
Dept. of Phys.
Univ. of Florida
P.O. Box 118440
Gainesville, FL, 32611- 8440, USA

Paul Maragakis
maragakis@cmt.harvard.edu
Dept. Chem. and Chemical Biol.
Harvard Univ.
12 Oxford St.
Cambridge, MA 02138, USA

Janna K. Maranas
jmaranas@psu.edu
Dept. of Chemical Engineering
The Pennsylvania State University
University Park, PA 16802, USA

Kim McClure
kim.f.mcclure@pfizer.com
Pfizer Global R&D
Eastern Point Rd
Groton, CT, 06340 USA

S. Miertus
International Cent. For
Sci. and High Tech.
UNIDO, AREA Science Park
Padriciano 99
I-34012 Trieste, Italy

W. Mooij,
w.mooij@astex-therapeutics.com
Astex Therapeutics Ltd.
436 Cambridge Science Park
Milton Road, Cambridge
CB4 0QA United Kingdom

Prof. Henriette Molinari
molinari@sci.univr.it
Dipt. Scientifico e Tecnologico
Univ. di Verona
Ca' Vignal 1, Strada le Grazie 15,
37134, Verona, Italy.

Marco Mor
Dept. Farma.
Univ. degli Stu. di Parma
Parco Area delle Scienze 27/A
I-43100 Parma, Italy

Adrian J. Mulholland
Centre for Comp. Chem.
School of Chemistry
Univ. Bristol
Cantock's Close, Bristol BS8 1TS,
U. K.

Martin H. Müser
mmuser@uwo.ca
Dept. of Applied Mathematics
University of Western Ontario
London, Ontario N6A 5B7, Canada

Tam Nguyen
nguyent@ncifcrf.gov
Developmental Therapeutics.
National Cancer Instit.
Frederick, MD 21702, USA
Jan Norberg
Cent. for Stru. Biochem.
Dept. of Biosci. at Novum
Karolinska Inst.
SE-141 57 Huddinge, Sweden

Ruth Nussinov
ruthn@ncifcrf.gov
NCIFrederick
Bldg. 469, Rm 151
Frederick, MD 21702, USA.

Toru Oba
Inst. for Mol.Sci.
Okazaki
Aichi 444-8585, Japan

Juan J. de Pablo
depablo@engr.wisc.edu
Dept. of Chem. and Biol. Eng.
Univ. of Wisconsin–Madison
1415 Engineering Drive
Madison, WI 53706–1691, USA.

Vijay S. Pande
pande@stanford.edu
Department of Chemistry and
Structural Biology
Stanford University
Stanford, CA 94305-5080, USA

Hwangseo Park
hwangseo@snu.ac.kr
Dept. of Chem.
Seoul Natl. Univ.
Seoul 151-747, South Korea

Nagarajan Pattabiraman
np47@georgetown.edu
Dept. of Biochem. & Molec. Biol.
and Dept. of Oncology
Lombardi Comprehensive Cancer
Center, Georgetown Univ.
NRB, Room W417 3970,
Reservoir Rd
NW Washington, DC, 20005, USA

Florencio Pazos
pazos@cnb.uam.es
Structural Bioinformatics Group
Division Mol. Biosciences
Imperial College London
London SW7 2AZ, UK

Igor Polikarpov
ipolikarpov@if.sc.usp.br
Instituto de Física de São Carlos
Universidade de São Paulo
São Carlos SP 13560-970, Brazil

Rama Ranganathan
rama.ranganathan@utsouthwestern.edu
Dept. Biochemistry
Univ. Texas Southwestern
Medical Center
Dallas, TX 75390, USA

Nigel G. J. Richards
Dept. of Chem.
Univ. of Florida
Gainesville, Florida 32611-7200

George D. Rose
grose@jhu.edu
T. C. Jenkins Dept. of Biophys.
The Johns Hopkins Univ.
3400 N. Charles Street
Baltimore, MD 21218-2608, USA.

Burkhard Rost
rost@cubic.bioc.columbia.edu
CUBIC, Dept. of Biochem.
and Molec. Biophys.
Columbia Univ.
630 West 168th Street, BB217,
New York, NY 10032, USA.

Carme Rovira
crovira@pcb.ub.es
Centre de Recerca
en Química Teòrica
Parc Científic de Barcelona
Barcelona, Spain

Harold A. Scheraga
Baker Lab. Chem. & Chem. Biol.
Cornell Univ.
Ithaca, NY 14853-1301, USA.
has5@cornell.edu

Franz Schmid
fx.schmid@uni-bayreuth.de
Laboratorium für Biochemie
Univ. Bayreuth
D-95440 Bayreuth, Germany

Klaus Schulten
kschulte@ks.uiuc.edu
Beckman Institute
Univ. of Illinois at
Urbana-Champaign
Urbana, IL 61801, USA

Tamar Schlick
schlick@nyu.edu
Dept. of Chem.
251 Mercer St.
New York Univ.
New York, NY. 10012, USA

Steven D. Schwatrz
sschwartz@aecom.yu.edu
Dept. of Physiology and Biophys.
Albert Einstein College of
Medicine
1300 Morris Park Ave
Bronx, NY 10461, USA

J. E. Shea
shea@chem.ucsb.edu
Dept. of Chem. and Biochemistry
University of California
Santa Barbara, CA, USA

Carlos Simmerling
carlos.simmerling@stonybrook.edu
Dept. of Chem.
Stony Brook Univ.
Stony Brook, NY 11794, USA

Munir S. Skaf
skaf@iqm.unicamp.br
Instituto de Química
Univ. Estadual de Campinas
Campinas SP 13084-862, Brazil

Walter Thiel
thiel@mpi-muelheim.mpg.de
Max-Planck-Inst fur
Kohlenforschung
D-45470 Mulheim an der Ruhr,
Germany

Julie D. Thompson
poch@igbmc.u-strasbg.fr
Dépt. de Biol. et Génom. Struct.
Inst. de Génét. et de Biol. Molcul.
et Cellul. (CNRS/INSERM/ULP)
BP 10142
67404 Illkirch Cedex, France.

G. Tiana
Dept. di Fisica
Univ. di Milano, and INFN
via Celoria 16
20133, Milano, Italy

D. Peter Tieleman
tieleman@ucalgary.ca
Dept. of Biological Sci.
Univ. Calgary
2500 University Dr NW
Calgary, Alberta, T2N 1N4,
Canada

Joanna Trylska
joanna@icm.edu.pl
ICM Warsaw University
Zwirki i Wigury 93
02-089 Warsaw, Poland

Wilfred F. van Gunsteren
wfvgn@igc.phys.chem.ethz.ch
Laboratory of Physical Chemistry
Swiss Fed. Inst. of Tech. Zürich
ETH-Hönggerberg
CH-8093 Zürich, Switzerland

Flavia Varano
Dept. di Sci. Pharm.
Univ. degli Stu. di Firenze
Polo Scientifico
via Ugo Schiff, 6,
50019 Sesto Fiorentino (FI), Italy

Michele Vendruscolo
mv245@cam.ac.uk
Dept. Chemistry
Univ. Cambridge
Lensfield Rd.
Cambridge CB2 1EW, UK

Nico Vermeulen
npe.vermeulen@few.vu.nl
Vrije Universiteit
De Boelelaan 1083
1081 HV Amsterdam
The Netherlands

Fernando Vericat
vericat@iflysib.unlp.edu.ar
Instituto de Física de Líquidos y
Sistemas Biológicos (IFLYSIB)-
Consejo Nacional de Inv.
Científicas y Técnicas-
Universidad Nacional de La Plata
(CONICET-UNLP)
1900 La Plata, Argentina
and
Grupo de Aplicaciones
Matemáticas y Estadísticas de la
Facultad de Ingeniería (GAMEFI)
Facultad de Ingeniería
Univ. Nac. de La Plata (UNLP)
1900 La Plata, Argentina

Jordi Villà-Freixa
jvilla@imim.es
Comp. Biochem. Biophys. Lab.
Research Group on
Biomedical Informatics (GRIB)
Inst. Municipal d'Investigació Mèd.
and Universitat Pompeu Fabra
C/Doctor Aiguader
80 08003 Barcelona,
Catalunya, Spain

Gregory A. Voth
voth@chem.utah.edu
Center for Biophysical Modeling
and Simulation and
Department of Chemistry
University of Utah
Salt Lake City, UT 84112-0850,
USA

Anna Vulpetti
anna.vulpetti@nervianoms.com
Nerviano Medical Sciences
Viale Pasteur 10
20014 Nerviano, Italy

Shaomeng Wang
shaomeng@umich.edu
Dept. Medicinal Chem.
Univ. Michigan
1500 E. Medical Center Dr.
Ann Arbor, MI 48109, USA

Jerome Wielens
jerome.wielens@
vcp.monash.edu.au
Dept. of Medicinal Chem.
Monash Univ.
381 Royal Parade
3052, Parkville, Vic., Australia.

Harel Weinstein
haw2002@med.cornell.edu
Dept. Physiology and Biophys.
Weill Medical College of Cornell
Univ
1300 York Ave
New York, NY 10021, USA

Jimin Xie
Sch. of Chem. & Chem. Engg.
Jiangsu Univ.
Zhenjiang 212013, PR China

Huan-Xiang Zhou
zhou@sb.fsu.edu
Dept. of Phys. and Inst. of Molec.
Biophys. and Sch. of Comput. Sci.
Florida State Univ.
Tallahassee, FL 32306, USA.

Jan Zielkiewicz
jaz@chem.pg.gda.pl
Department of Chemistry
Gdańsk University of Technology
Narutowicza 11/12
Gdańsk 80-952, Poland

5. DISCLAIMER, COPYRIGHT, AND PUBLISHER INFORMATION

MMCC Results (ISSN 1061-6381), published by MMCC Results, 706 Sunny Lane, Orem, Utah 84058, is a private business independent of all software and hardware vendors, companies, government laboratories, universities, and other institutions whose products or publications may be cited herein. David D. Busath, M.D. is Professor of Physiology and Biophysics, Dept. of Physiology and Developmental Biology, Brigham Young University. Mention of a software product is for information purposes only and does not constitute an endorsement or recommendation by either MMCC Publishing or the authors of the paper cited. All product names are the trademarks or registered symbols of their respective organizations.

Copyright (c) 2005 by MMCC Publishing.

MMCC Results is published ten times per year, at the beginning of each month except January and August. For subscription information, please contact MMCC Publishing:

Editor:

David Busath, M.D.	Tel. (801) 422-8753
MMCC Results	FAX (801) 422-0700
706 W. Sunny Lane	E-mail: mmcc@itsnet.com
Orem, Utah 84058	

Bruce Gelin, founder and editor of MMCC Results Volumes 1-6, is Editor Emeritus.

Associate Editor:
Thomas Cheatham, Depts. of Med. Chem. & of Pharmaceutics & Pharm. Chem., Univ. of Utah, Salt Lake City, UT.

Assistant Editors:
Alan C. Cheng, Pfizer Global R&D, Cambridge, MA
Anton Feenstra, Vrije Univ., Amsterdam, Netherlands
R. Nageswara Ramireddy, Genomik Design Pharmaceut. Pvt. Ltd., Hyderabad, India