Results

MOLECULAR MODELING & COMPUTATIONAL CHEMISTRY

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Editorial and News

We are excited to bring you another year of MMCC Results, the molecular modeling newsletter. When I took over this project from Bruce Gelin seven years ago, I could not forsee how steady the need would be for this service. But the subscription base for the newsletter, which consists of most of the major pharmaceutical companies and many academic scientists, remains solid. Last year I experimented by broadening the base of sources for the materials in the newsletter and the results seem to have been very successful.

This year, we will continue the tradition. You will notice that we have enhanced our coverage by adding short reviews (under the Journal Reviews section) for lateral articles from *JACS* and *JPCB.* Also, the new ACS journal, *Journal of Chemical Theory and Computation,* will be fully covered. *J. Chem. Phys.* has shifted to the *Physical Review*s style for page numbering, and we will use the same adaptation we have used in the past with *Phys. Rev.,* which is designed to accommodate reference database programs.

Macromolecular MD is an art form with an experimental flavor. Skill and judgement, which come from extensive experience, are required to know which questions can be successfully answered and which cannot. As the past three decades have shown, this discipline continues to increase in practice and value, with continually increasing understanding on the part of practitioners of the merits and limitations.

This newsletter is dedicated to the diffusion of knowledge about this complex scientific arena. Still often dismissed by knowledgable structural biologists, we must humbly acknowledge the weaknesses in our force fields, the sampling limitations imposed by our algorithms, and the potential for erroneous conclusions, interpretations, and assumptions. But at the same time, our readers see the evidence in each issue of the success of simulations and their merit. It's a lot like weather forecasting. Everybody curses the weatherman, but carefully watches the forecast.

David D. Busath, Editor

1. APPLICATIONS

1.1. *Small Molecules*

General and Model Systems

Tuning of hydrogen bond strength using substituents on phenol and aniline: A possible ligand design strategy

J Reynisson and E McDonald* [Inst Cancer Res, Sutton]

J Comput Aided Mol Des **18**, 421-431 (2004)

Detailed structural and energetic analysis of DFT calculations of various substituted phenols and anilines shows negligible effects on neutral compounds, but significantly stronger effects on charged compounds. Comparison with existing, approximate, measures is made.

Theoretical calculations of homoconjugation equilibrium constants in systems modeling acid-base interactions in side chains of biomolecules using the potential of mean force.

J. Makowska, M. Makowski* [U Gdańsk], A. Liwo, and L. Chmurzyski

J. Comput. Chem. **26,** 235-242 (2005)

The free energies of conjugation via OHO or HNH bridges for a small set of acids and amines was computed using WHAM. OHO bridges gave higher binding affinity than HNH bridges. The binding affinity decreases with solvent polarity (Acetonitrile > DMSO > H_2O).

Single particle dynamics in ionic liquids of 1-alkyl-3-methylimidazolium cations.

S. M. Urahata and M.C.C. Ribeiro

J. Chem. Phys. **122,** 02451101-02451109 (2005)

In molten imidazole-derivative salts with anions of various sizes, the organic cations are actually more mobile than the anions, according to MD simulations. The alkyl chains, ranging from 1-8 carbons, form an axis. Dominant cation motion is perpendicular to this axis.

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Dr. Gelin was founder of MMCC Results and edited volumes 1-6.

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Water and Solvation

Ion solubility in ice: Calculation of potentially favorable positions of Cl^- and Na^+ ions in the SPC/E model of ice 1 h*.

E.J. Smith* [U Houston] and A.D.J. Haymet

Mol. Sim. **30**, 827-830 (2004)

MD simulations are used to investigate the favorable and unfavorable locations for positive and negative ions in the ice 1 h lattice. This is the first step to calculate the solubility of ions in ice as distinct from liquid water.

Temperature dependence of three-body hydrophobic interactions: Potential of mean force, enthalpy, entropy, heat capacity, and nonadditivity.

M.S. Moghaddam, S. Shimizu, and H.S. Chan* [U Toronto]

J. Amer. Chem. Soc. **127**, 303-316 (2005)

Extensive simulation of the PMF of methane-like nonpolar solutes in TIP4P water at multiple temperatures gives insight into the hydrophobic interaction. An interesting observation is the negative heat capacity resulting from burial of exposed hydrophobic surface area. The implications for protein folding are discussed.

Hydroxyl radical at the air-water interface.

M. Roeselova, J. Vieceli, L.X. Dang, B.C. Garrett, and D.J. Tobias* [UCI]

J. Amer. Chem. Soc. **126**, 16308-16309 (2004)

MD simulation is performed on five hydroxyl molecules embedded in a water slab surrounded by a vacuum interface. The results provide insight into the transfer of the OH radical across the air-water interface.

Molecular dynamics simulation study on the transient response of solvation structure during the translational diffusion of solute.

T. Yamaguchi* [Nagoya U], T. Matsuoka, and S. Koda

J. Chem. Phys. **122,** 01451201-01451210 (2005)

During translational diffusion, larger cations and neutral solutes show behaviors in water expected from theories for simple solvents, whereas for Li+ the inner shell undergoes underdamped, high frequency oscillations that may affect mobility.

Dependence of ion hydration on the sign of the ion's charge.

A. Grossfield* [Washington U]

J. Chem. Phys. **122,** 02450601-02450610 (2005)

With a polarizable force field, MD simulations indicate that anion hydration is better than cation hydration due to improved interactions of first shell water with second shell waters.

Organic Solvents

Investigation of structure of liquid 2,2,2 trifluoroethanol: Neutron diffraction, molecular dynamics, and ab initio quantum chemical study.

I. Bakó* [Hungarian Acad Sci], T. Radnai, and M.C.B. Funel

J. Chem. Phys. **26,** 12472-12480 (2004)

Trifluoroethanol has smaller hydrogen bonded aggregates than ethanol.

Medicinal Chemistry and Drug Design

Molecular dynamics simulations of 14 HIV protease mutants in complexes with indinavir.

X. Chen, I.T. Weber* [Georgia Sate U], and R.W. Harrison
J. Mol. Mod. **10**, 373-381 (2004)

MD simulations are applied to study the molecular mechanisms of HIV drug resistance between the HIV-1 protease and the indinavir inhibitor. The averaged molecular mechanics interaction energy gave the protease affinity for indinavir. The correlation coefficient and observed inhibition constants for wild type and four mutants are in good agreement.

Taking aim at a moving target: designing drugs to inhibit drug-resistant HIV-1 reverse transcriptases.

S.G. Sarafianos, K. Das, S.H. Hughes,
and E. Arnold* [Rutgers U]

Curr. Opi. Str. Biol. **31**, 716-730 (2005)

Two broad strategies are approached for hitting a moving target for anti-HIV drug. Firstly, understanding the mechanisms of drug resistance and developing drugs that effectively inhibit mutant viruses. Secondly, designing drugs that interact with portions of the viral machinery that are evolutionarily conserved, such as enzyme active sites.

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Identification of novel parasitic cysteine protease inhibitors using virtual screening. 1. The ChemBridge database.

P.V. Desai, A. Patny, Y. Sabnis, B. Tekwani, J. Gut,
P. Rosenthal, A. Srivastava, and M. Avery* [U Mississippi]

J. Med. Chem. **47,** 6609 - 6615 (2004)

The 241k compound ChemBridge database was filtered for drug-like properties, resulting in 60k compounds which were docked into falcipain-2 and falcipain-3. Of the 200 top dock hits, 84 were tested and 22 compounds were found to inhibit one of the falcipains with an IC50 of 1-63 uM.

Interaction profiles of protein kinase-inhibitor complexes and their application to virtual screening.

C. Chuaqui, Z. Deng, and J. Singh* [Biogen-Idec]

J. Med. Chem. **48,** 121-133 (2005)

A set of 54 kinase inhibitor co-crystal structures are clustered into the p38, CDK2, and ATP analogue groups. A histogram plot of the frequency of interactions to key kinase residues provides easy visualization of residues providing specificity differences, and this "interaction profile" of frequencies can be used to bias virtual screening hits to known inhibitor binding modes, or alternatively, identifying "novel" docked binding modes

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HIV-reverse transcriptase inhibition: Inclusion of ligand-induced fit by cross-docking studies.

R. Ragno* [U Roma], S. Frasca, F. Manetti, A. Brizzi,
and S. Massa* [U Siena]

J. Med. Chem. **48,** 200-212 (2005)

Autodock was shown to be effective in redocking 41 known NNRTI (non-nucleoside reverse transcriptase inhibitor) co-crystal structures. Known conformations in 98% of the cases were replicated within a RMSD of <2.0A. Cross-docking is suggested as useful in accounting for protein flexibility as well as spectrum against mutated HIV RT proteins.

ZINC - A free database of commercially available compounds for virtual screening.

J.J. Irwin and B.K. Shoichet* [UCSF]

J. Chem. Inf. Model. **45,** 177-182 (2005)

A free downloadable database of 728k orderable compounds prepared for docking is available at http://zinc.docking.org. For each compound, the database provides a 3D structure, multiple conformations, protonation states, and tautomeric forms.

Measuring CAMD technique performance: A virtual screening case study in the design of validation experiments

M.A.H.A.C. Good* [Bristol-Myers Squibb] and S.A. Hindle

J Comput Aided Mol Des **18**, 529-536 (2004)

A relatively thorough and 'real-life-like' evaluation of several commonly used ligand-based screening methods is presented and tested on Melatonin receptor, AP2, CDK2 and FXa. No one method performs best throughout mainly caused by different chemical variations within the targets' inhibitors.

Quantitative Structure-Activity Relations

A topological sub-structural approach for predicting human intestinal absorption of drugs.

M.A.C. Pérez* [Cent U Las Villas], M.B. Sanz, L.R. Torres, R.G. Ávalos, M.P. González, and H.G. Díaz

Eur. J. Med. Chem. **39**, 905-916 (2004)

The TOPS-MODE approach is used to study the human intestinal absorption of drugs. The positive and negative sub-structural contributions to the HIA were identified and evaluated for their possibilities in the lead generation and optimization process.

Investigation of structure-activity relationships in a series of glibenclamide analogues.

E. Yuriev, D.C.M. Kong, and M.N. Iskander* [Monash U]

Eur. J. Med. Chem. **39**, 835-847 (2004)

3D-QSAR is used to study the compounds' ability to antagonize the [^{3}H]-glibenclamide binding in rat cerebral cortex. CoMFA models showed that the steric and lipophilic properties are the major interacting forces and the electrostatic property contribution was a minor factor.

Quantitative structure activity relationship studies of diaryl furanones as selective COX-2 inhibitors.

S. Shahapurkar, T. Pandya, N. Kawathekar, and S.C. Chaturvedi* [Devi Ahilya Vishwavidyalaya]

Eur. J. Med. Chem.**39**, 899-904 (2004)

MOE

The Molecular Operating Environment is used for QSAR studies of 43 analogues of COX-2. These studies gave significant correlations of selective inhibitors with physical property, connectivity and conformation of molecule. COX-1 inhibitory data was analyzed with the descriptors and gave significant results for physico-chemical properties.

Structure-activity relationships for 1-alkyl-3-(1-naphthoyl) indoles at the cannabinoid CB_1 and CB_2 receptors: Steric and electronic effects of naphthoyl substituents. New highly selective CB_2 receptor agonists.

J.W. Huffman* [Clemson U], G. Zengin, M.J. Wu, J. Lu, G. Hynd, K. Bushell, A.L.S. Thompson, S. Bushell, C. Tartal, D.P. Hurst, P.H. Reggio, D.E. Selley, M.P. Cassidy, J.L. Wiley, and B.R. Martin

Bioorg. Med. Chem. **13,** 89-112 (2005)

Molecular modeling and receptor docking studies indicated that the CB_1 receptor affinities of indole derivatives were consistent with their aromatic stacking interactions in the aromatic microdomain of the CB_1 receptor.

Quantitative Structure-Activity Relationships (cont'd)

On the role of polarizability in QSAR.

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

Bioorg. Med. Chem. **13,** 237-255 (2005

The polarizability effects on ligand–substrate interactions are described in terms of NVE (number of valence electrons) using additive values for valence electrons. The QSAR model is illustrated by the equation $\log 1/C = a(\mathrm{NVE}) \pm \mathrm{constant}$.

QSAR analyses on ginkgolides and their analogues using CoMFA, CoMSIA, and HQSAR

W. Zhu, G. Chen, L. Hu, X. Luo, C. Gui, C. Luo, C.. Mok Puah, K. Chen, and H. Jiang* [Chinese Acad Sci]

Bioorg. Med. Chem. **13**, 313-322 (2005)

CoMFA, CoMSIA, and HQSAR methods are used to investigate the relationship between 117 ginkgolide analogues with great structural diversity and their bioactivities against PAF receptor. These models showed how steric, electrostatic, hydrophobicity, and individual atom type affected molecular bioactivity as antagonists of PAF. The results are useful for discovering new drugs as PAF antagonists in fighting against various diseases related to PAF and PAF receptor.

Application of QSAR analysis to organic anion transporting polypeptide 1a5 (Oatp1a5) substrates.

M. Yarim* [ETH Zurich], S. Moro, R. Huber, P.J. Meier, C. Kaseda, T. Kashima, B. Hagenbuch, and G. Folkers

Bioorg. Med. Chem. **13**, 333-341 (2005).

3D-QSAR is used to obtain topological information on the substrate binding-site of the protein. The Genetic Algorithm Similarity Program and CoMFA were used for structural alignment of the heterogeneous data set of 18 Oatp1a5 substrates. The results of this model identified new potential Oatp1a5 substrates and their predicted apparent affinity values were confirmed experimentally.

Predicting anti-HIV activity of 2,3-diaryl-1,3-thiazolidin-4-ones: computational approach using reformed *eccentric connectivity index.*

V. Kumar, S. Satish, and M.A. Kumar* [MD U]

J. Mol. Mod. **10**, 399 -407 (2004)

The relationship was investigated between the eccentric connectivity topochemical index, eccentric connectivity index and Wieners's index with respect to the anti-HIV activity of 2, 3-diaryl-1, 3-thiazolidin-4-one derivatives. An in-house program was used for the data set analysis. The biological activity for each derivative was compared with the reported anti-HIV activity. The proposed index offers a vast potential for virtual screening of combinatorial libraries, structure property/activity studies and drug design.

Antileishmanial activity, cytotoxicity and QSAR analysis of synthetic dihydrobenzofuran lignans and related benzofurans.

S.V. Miert, S.V. Dyck, T.J. Schmidt, R. Brun, A. Vlietinck, G. Lemière and L. Pieters* [U Antwerp]

Bioorg. Med. Chem. **14**, 661-669 (2005)

Quasar receptor surface modeling is used to generate QSAR models for the cytotoxic and antileishmanial activity.

Quantitative Structure-Activity Relationships (cont'd)

3D-QSAR illusions.

M.D. Arthur* [Bristol-Myers Squibb]

J Comput Aided Mol Des **18**, 587-596 (2004)

A thorough evaluation of a 'random' sample of published 3D-QSAR models is presented. In spite of aiming for predictivity, most models are retrospective (even a q^2 of 0.9 can give predictions with r^2's ranging from 0 (sic!) to 1) and significance of interaction regions derived from aligned compounds is questionable at best. Alignment based on receptor structure (e.g., docked compounds) can yield much more meaningful results.

Carbon Adsorbent

An effective potential for adsorption of polar molecules on graphite.

X. Zhao* [U Pittsburgh] and J.K. Johnson

Mol. Sim. **31**, 1-10 (2005)

An approximate method is proposed for accounting for the change in the solid-fluid potential energy due to polar interactions with graphite. The potential function is integrated over the graphite surface using a truncated Fourier series with dipole-induced dipole, dipole-quadrupole, and quadrupole-quadrupole interactions. This potential is used for fluid molecules with dipole and/or quadrupole moments.

Zeolites

Diffusivity of CH_4 in model silica nanopores: Molecular dynamics and quasichemical mean field theory.

G.K. Papadopoulos* [Nat Tech U Athens]

Mol. Sim. **31**, 57-66 (2005)

Equilibrium MD and grand canonical MD simulations were applied to investigate the dependence of transport diffusivity upon the adsorbent pore size and sorbate concentration of CH_4 in cylindrical silica nanopores. Sorbate-sorbate energetics emerge as the physical reason for the variation of corrected transport diffusivity with respect to pore size and sorbed phase fractional occupancy.

Carbon Nanoparticles

Molecular simulation for nanotechnologies: Application to industry.

Y. Hiwatari* [Kanazawa U], Y. Kaneko, and H. Ishida

Mol. Sim. **30**, 819-826 (2004)

The electrodeposition in nano-scales and martensite transformation are studied to solve real problems existing in industries. Firstly, a coarse-grained, or smart, model was developed to study the electrodeposition. Secondly, how the atomistic model can be predictable the martensite transformation in bulk was discussed.

1.2. *Biopolymers*

Bioinformatics

Implications of structural genomics target selection strategies: Pfam5000, whole genome, and random approaches

J.M. Chandonia and S.E. Brenner* [U Calif Berkeley]

Proteins **58**, 166-179 (2005)

A thorough comparison in overall efficiency of different structural genomics target selection schemes, with respect to covering protein-family or -fold space, is presented. Pfam5000 and random selection would result in roughly similar coverage, while a whole genome approach would be much less efficient.

PhosphaBase: an ontology-driven database resource for protein phosphatases

K.J. Wolstencroft* [U Manchester], R. Stevens, L. Tabernero, and A. Brass

Proteins **58**, 290-294 (2005)

The setup and building of a database for the protein phosphatase family, drawing from automated and expert data acquisition based on gene ontologies, is described. Data extraction and possible future use are discussed.

Predicting protein functional sites with phylogenetic motifs

D. La, B. Sutch, and D.R. Livesay* [Calif State Polytech U]

Proteins **58**, 309-320 (2005)

Phylogenetic motifs, derived from phylogenetic trees, are used to identify functional sites in 15 protein families (~1000 sequences) and shown to perform rather well in spite of absence of sequence homology in several cases.

Classification of a large anticancer data set by Adaptive Fuzzy Partition

N. Piclin, M. Pintore, C. Wechman, and J.R. Chrétien* [U Orleans]

J Comput Aided Mol Des **18**, 577-586 (2004)

Ambitious application of AFP is used to classify automatically anticancer drugs in a virtual screening setup. The model was trained on 640 compounds, validated on 280 and tested on 374. On average 70-90% are classified correctly.

Protein Sequence Analysis and Alignment

Principal eigenvector of contact matrices and hydrophobicity profiles in proteins

U. Bastolla* [INTACSIC Madrid], M. Porto, H.E. Roman, and M. Vendruscolo

Proteins **58**, 22-30 (2005)

The principal Eigenvector of the contact matrix and the hydrophobicity profile are shown to correlate significantly for many sequences in seven protein families, and even stronger for the family average profile. Chain-length dependent effects and evolutionary implications are discussed.

A generalized affine gap model significantly improves protein sequence alignment accuracy

M.A. Zachariah, G.E. Crooks, S.R. Holbrook, and S.E. Brenner* [U Berkeley]

Proteins **58**, 329-338 (2005)

A systematic evaluation of affine gap penalties on remote homology detection is presented. At the cost of fewer total aligned residue-pairs, per-residue accuracy can be increased.

Protein Structure Prediction

Sequence patterns associated with disordered regions in proteins

S. Lise* [U Coll London] and D.T. Jones

Proteins **58**, 144-150 (2005)

A rather straightforward statistical analysis of globular and disordered proteins reveals several significant patterns of amino acid types as well as amino acid property types.

Predictive in silico all-atom folding of a four-helix protein with a free-energy model.

A. Schug and W. Wenzel* [Forsch Karlsruhe]

J. Amer. Chem. Soc. **126**, 16736-16737 (2004)

Monte Carlo and simulated annealing of various lengths of the sequence in an all-atom model were performed using a simple, distributed, evolutionary strategy as a means to predict protein structure. The protein studied is a 60-amino acid fource helix protein, one of the largest predicted to-date at the all-atom level.

Comparative or Homology Modeling

Homology modelling and binding site mapping of the human histamine H1 receptor.

R. Kiss, Z. Kovári, and G.M. Keserű* [Gedeon Richter Ltd.]

Eur. J. Med. Chem. **39**, 959-967 (2004)

The high-resolution structure of bovine rhodopsin is used to develop the 3D-model of the human histamine H1 receptor. Genetic algorithm based docking calculations were used to identify the role of several amino acids having an effect on agonist or antagonist binding.

Modeling the *E. coli* 4-hydroxybenzoic acid oligoprenyl-transferase (*ubiA* transferase) and characterization of potential active sites.

L. Bräuer, W. Brandt,
and L.A. Wessjohann* [Leibniz Inst of Plant Biochem]

J. Mol. Mod. **10**, 317-327 (2004)

Homology modeling techniques are used to develop a model with two putative active sites. Semiempirical quantum mechanical PM3 calculations are used to investigate the thermodynamics and kinetics of the catalysis mechanism. The results suggested a near S_N1 mechanism for the cleavage of the diphosphate ion from the isoprenyl unit.

Homology models of the cannabinoid CB1 and CB2 receptors. A docking analysis study.

C. Montero, N.E. Campillo, P. Goya,
and J.A. Páez* [CSIC]

Eur. J. Med. Chem. **40**, 75-83 (2005)

The cannabinoid system was studied by docking techniques, using the 3D models of both CB1 and CB2 and well-known reference inverse agonist/antagonist compounds. The structural effects of ligand binding were studied and analyzed on the basis of hydrogen bond interactions, and binding energy calculations.

Issues in high-throughput comparative modelling: a case study using the ubiquitin E2 conjugating enzymes

PJ Winn* [EMBL], J.N. Battey, K. Schleinkofer,
A. Banerjee, and R.C. Wade

Proteins **58**, 367-375 (2005)

An automated homology modeling 'pipeline' for UBC enzymes is presented. The use of multiple templates was discarded for lack of detectable improvement, reverting to the single highest-homologues template. Rotamer and H-bond network optimization are discussed.

Peptide Conformational Analysis

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Equilibrium structure and folding of a helix-forming peptide: Circular dichroism measurements and replica-exchange molecular dynamics simulations.

G.S. Jas* [U Kansas] and K. Kuczera* [U Kansas]

Biophys. J. **87,** 3786-3798 (2004)

MD simulations of a 21-residue peptide that forms helices at temperatures just below room temperature show that, from the extended state, the peptide becomes helical after about 2 ns and reaches equilibrium after about 10 ns. Folding involves increasing the number of backbone hydrogen bonds. The computed enthalpy and entropy of folding are –10 kcal/mol and entropy of –30 cal/(mol K), similar to the measured values of –11.6 kcal/mol and –39.6 cal/(mol K).

Energy landscape of a small peptide revealed by dihedral angle principal component analysis

Y. Mu* [Nanyang Techn U], P.H. Nguyen,
and G. Stock* [Goethe U]

Proteins **58***,* 45-52 (2005)

Analysis of PC in dihedral space reveals a rugged free energy landscape with many well-defined minima, in contrast to the smooth funnel-shaped free energy landscape in Cartesian space. Implications for protein folding are discussed.

Early events in protein aggregation: molecular flexibility and hydrophobicity/charge interaction in amyloid peptides as studied by molecular dynamics simulations

M. Valerio, A. Colosimo, F. Conti, A. Giuliani, A. Grottesi,
C. Manetti, and J.P. Zbilut* [Rush Med Coll]

Proteins **58***,* 110-118 (2005)

Differences in conformational flexibility of two peptides, Aβ(1-28) and Aβ(1-40), from simulations at their isoelectric points where they are neutral and most flexible, explain differences in aggregation propensity.

Long-time conformational transitions of alanine dipeptide in aqueous solution: continuous and discrete-state kinetic models.

D.S. Chekmarev, T. Ishida, and R.M. Levy* [Rutgers U]

J. Phys. Chem. B **108**, 19487-19495 (2004)

Long time scale GB simulations of the alanine dipeptide in the context of the OPLS force field investigate the dynamics and time scales for conformational interchange. A detailed presentation is provided with ample discussion of the kinetic models and implications for the study of larger peptides.

Folding Trp-Cage to NMR resolution native structure using a coarse-grained protein model.

F. Ding* [U N Carolina Chapel Hill], S.V. Buldyrev, and
N.V. Dokholyan* [U N Carolina Chapel Hill]

Biophys. J. **88,** 147-155 (2005)

A simplified force field based on residue-residue interaction energies is sufficient to produce consistent folding of the 20-residue Trp cage protein to within 2 Å of the NMR structure.

Protein Structure Analysis

Structural classification of thioredoxin-like fold proteins

Y. Qi and N.V. Grishin* [U Texas]

Proteins **58**, 376-388 (2005)

723 protein domains with thioredoxin-fold (including circular permutations) are identified from the PDB, and classified into 11 families, which unifies 5 SCOP, 5 CATH and 7 DALI classes. Some folds identified by the database search, were rejected based on more stringent topological considerations.

Analysis of pH-dependent elements in proteins: geometry and properties of pairs of hydrogen-bonded carboxylic acid side-chains

G. Wohlfahrt* [Orion Pharma]

Proteins **58**, 396-406 (2005)

Combining analysis of carboxylic acid pairs in x-ray structures and QM calculations of these pairs in dielectric medium, show consistent trends and indicate involvement in low-pH and high(er) temperature protein stability. Possible implications for (rational) protein design are discussed.

Molego-based definition of the architecture and specificity of metal-binding sites

C.H. Schein* [U Texas], B. Zhou, N. Oezguen, V.S. Mathura, and W. Braun

Proteins **58**, 200-210 (2005)

An automated method to define structural-chemical motifs is applied to identify metal binding sites in dimetallic phosphatases, DNAse 1 homologues and dioxygenases. Motifs obtained were able to filter similar sites from the ASTRAL40 database. The functional significance of these motifs is discussed.

Existence of specific "folds" in polyproline II ensembles of an "unfolded" alanine peptide detected by molecular dynamics.

V. Ramakrishnan, R. Ranbhor, and S. Durani* [ITT Bombay]

J. Amer. Chem. Soc. **126**, 16332-16333 (2004)

MD simulations of octa-alanine peptides with the GROMOS96 force field display a strong polyproline II helix tendency. The tendency is claimed to relate to residue level preferences, however no experimental data is provided to justify that the simulation results are in fact "real".

Helical packing patterns in membrane and soluble proteins.

M. Gimpelev, L.R. Forrest, D. Murray, and B. Honig* [Columbia U]

Biophys. J. **87,** 4075-4086 (2004)

Membrane protein helices were compared to soluble proteins. Most regular transmembrane helices have decent homologs. Transmembrane proteins have close contacts primarily because of GXXG and AXXA motifs. Solubilization of membrane proteins by mutations with polar peripheral residues should frequently be feasible.

Protein Folding

Checking the pH-induced conformational transition of prion protein by molecular dynamics simulations: Effect of protonation of histidine residues.

E. Langella, R. Improta, and V. Barone* [U Federico II]

Biophys. J. **87,** 3623-3632 (2004)

Protonation of His residues in prion protein reduces helicity, increases beta character, helping to explain how H187R might be responsible for pathology.

Protein Folding (cont'd)

Probing the kinetics of single molecule protein folding.

V.B.P. Leite* [U Estadual Paulista], J.N. Onuchic, G. Stell, and J. Wang* [SUNY, Chinese Acad Sci]

Biophys. J. **87,** 3633-3641 (2004)

Moments of the first passage time are proposed as a helpful tool for analyzing folding trajectories. The transition from exponentially distributed folding times at high temperatures to more complex distributions at intermediate temperatures (due to multiple rate-limiting traps in the landscape) can be understoon in this context.

Kinetic pathways of ß-hairpin (un)folding in explicit solvent.

P.G. Bolhuis* [U Amsterdam]

Biophys. J. **88,** 50-61 (2005)

Folding of the C-terminal ß-hairpin in protein G-B1 always involves a layer or strip of water molecules between the two strands. The transition state ensembles are not always at saddle points in the free energy landscape: folding is partially under kinetic control. Calculated folding rates agree with experiment.

Protein folding in high-dimensional spaces: Hypergutters and the role of nonnative interactions.

T.C.B. McLeish* [U Leeds]

Biophys. J. **88,** 172-183 (2005)

The high dimensionality of protein folding begs the application of concepts from high-dimension topology. Some general conclusions are derived and illustrated with folding of a three-helix bundle. The main point seems to be that non-native contacts along the folding paths may play key roles, and that hyper-gutters can be important as well as the energy funnel.

Scaling of folding times with protein size.

A.N. Naganathan and W. Munoz* [U Maryland]

J. Amer. Chem. Soc. **127**, 480-481 (2005)

The folding of proteins occurs over time scales from microseconds to hours—9 orders of magnitude! In this communication, Munoz provides a simple scaling law that relates folding time to protein size.

Mapping long-range interactions in α-synuclein using spin-label NMR and ensemble molecular dynamics simulations.

M.M. Dedmon, K. Lindorff-Larsen, J. Christodoulou, M. Vendruscolo, and C.M. Dobson* [U Cambridge]

J. Amer. Chem. Soc. **127**, 476-477 (2005)

Ensemble MD simulations (with 20 replicas) incorporate paramagnetic relaxation enchancement NMR derived distance thresholds to study the unstructured protein α-synuclein. The results suggest a bimodal radius of gyration distribution and outline the long-range contacts between amino acids in the protein.

Characterization of the stereochemical selectivity of β-hairpin formation by molecular dynamic simulation.

P. Soto* [U Groningen], and R. Zangi

J. Phys. Chem. B **109**, 1281-1288 (2005)

MD simulations give insight into the structural effects of stereochemistry on β-hairpin formation with the GROMOS96 force field in explicit chloroform solvent (applying a twin range cutoff).

Protein Design and Engineering

Computational protein design is a challenge for implicit solvation models.

A. Jaramillo and S.J. Wodak* [U Libre de Bruxelles]

Biophys. J. **88,** 156-171 (2005)

Implicit solvent force fields (five were tested) do fairly well at discriminating native folds from non-native folds, but they have a harder time predicting residue burial. All but the crudest model yielded better burial of polar residues than nonpolar residues, leading to poor performance in protein design tasks.

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Protein Hydration

Partition of protein solvation into group contributions from molecular dynamics simulations

A. Morreale, X. de la Cruz*, T. Meyer, J.L. Gelpi, F.J. Luque, and M. Orozco* [U Barcelona]

Proteins **58***,* 101-109 (2005)

Based on MD simulations with explicit water, from linear response and a novel partitioning scheme with physical basis, fractional solvation terms for residues are derived. Results compare favorably with explicit MD simulations, and describe solvation effects in different parts of the protein. A comparison with a variety of existing methods is made.

Characterization of the denaturation of human alpha-lactalbumin in urea by molecular dynamics simulations

LJ Smith* [U Oxford], R.M. Jones, and W.F. van Gunsteren

Proteins **58***,* 439-449 (2005)

A detailed analysis of denaturation events and changes in H-bonding occurring during MD simulations of α-lactalbumin in explicit solvent of 6M urea in water at temperatures from 300-400 K is presented. Results match well with NMR-derived distance restraints at corresponding conditions. A complex mixture of different causes, including urea-induced inter-protein H-bonding, is observed.

Solvation influences flap collapse in HIV-1 protease

K.L. Meagher and H.A. Carlson* [U Michigan]

Proteins **58***,* 119-125 (2005)

Careful analysis of equilibration and solvation method effects during MD simulations shows reported HIV-flap closure dependent on system setup and equilibration method, the most carefully performed equilibration showing no flap closure and corresponding to NMR order parameters.

The effect of water displacement on binding thermodynamics: Concanavalin A.

Z. Li and T. Lazaridis* [CUNY]

J. Phys. Chem. B **109**, 662-670 (2005)

MD simulation probes the influence of a single water at the interface of a carbohydrate and the protein concanavalin A. Estimates of the entropy and enthalpy of this water agree well with experiment.

Intermolecular potentials of mean force of amino acid side chain interactions in aqueous medium.

S.A. Hassan* [NIH]

J. Phys. Chem. B **108**, 19501-19509 (2004)

MD simulations and PMF calculations of side chains in water show a set of 42 classes of representative hydrogen bonding interactions. The results have implications for development of implicit solvent models.

Protein Hydration (cont'd)

An application of coupled reference interaction site model/molecular dynamics to the conformational analysis of the alanine dipeptide.

H. Freedman* [U Utah] and T.N. Truong

J. Chem. Phys. **26,** 12447-12456 (2004)

For the RISM expression for solvation energy, a radial density function computed beforehand from an MD simulation is utilized with no iterations. The successful identification of the correct minimum energy conformation for alanine dipeptide suggests that the method may be useful in RISM applications to protein conformational search.

Protein Electrostatics and Titration

A molecular dynamics study of the structural stability of HIV-1 protease under physiological conditions: the role of Na+ ions in stabilizing the active site

D. Kovalskyy* [Inst Mol Biol & Gen Kiev], V. Dubyna, A.E. Mark, and A. Kornelyuk

Proteins **58***,* 450-458 (2005)

The effects of Asp protonation, ion binding and water insertion on the HIV-1 protease dimerization are studied with MD and ab-initio QM calculations. The single-protonated (1 Asp only) situation was most stable, with an additional Na+ bound. Stability is expected to decrease at low ionic strength.

Protein Dynamics

Origin of mechanical strength of bovine carbonic anhydrase studied by molecular dynamics simulation.

S. Ohta, M.T. Alam, H. Arakawa, and A. Ikai* [Tokyo Inst Tech]

Biophys. J. **87**, 4007-4020 (2004)

Steered MD indicates that the final peak in the force spectroscopy curve for CA unfolding is probably destruction of the zinc-coordinating core β-sheet.

Simultaneous determination of protein structure and dynamics.

K. Lindorff-Larsen, R.B. Best, M.A. Depristo, C.M. Dobson*[U Cambridge], and M. Vendruscolo* [U Cambridge]

Nature **433,** 128-132 (2005)

A new method of determining protein structure ensembles called DER (dynamic ensemble refinement) involves use of molecular dynamics as well as data from NMR relaxation experiments. Application of DER to ubiquitin finds that many side chains, including those in the core of the protein, have multiple rotameric states and "liquid-like" characteristics.

Efficient simulation method for polarizable protein force fields: Application to the simulation of BPTI in liquid water.

E. Harder, B. Kim, R.A. Friesner, and B.J. Berne* [Columbia U]

J. Chem. Theory Comput. **1,** 169-180 (2005)

An MD simulation of BPTI using a polarizable force field based on a combination of fluctuating charges and polarizable dipoles is only slightly slower than a similar simulation using a nonpolarizable force field. Differences in the results from the two types of MD simulations are highlighted.

Protein Dynamics (cont'd)

Changes in calmodulin main-chain dynamics upon ligand binding revealed by cross-correlated NMR relaxation measurements.

T. Wang, K.K. Frederick, T.I. Igumenova,
A.J. Wand* [U Penn], and E.R.P. Zuiderweg* [U Mich]

J. Amer. Chem. Soc. **127**, 828-829 (2005)

Very interesting NMR experiments, coupled with a simple harmonic model, definitively demonstrate changes in protein dynamics upon ligand binding. These sub-nanosecond motions could easily be investigated with modern MD simulation protocols as a means to aid in verification of the reliability of the current methods and force fields.

Methyl group dynamics as a probe of the protein dynamical transition.

J.E. Curtis, M. Tarek, and D.J. Tobias* [UCI]

J. Amer. Chem. Soc. **126**, 15928-15929 (2004)

MD simulations of RNase under various hydrating conditions (ranging from a dry powder to free in solution) at multiple temperature probes the influence of the methyl group dynamics above and below the glass transition state.

Ligand Binding

Searching for new allosteric sites in enzymes

J.A. Hardy and J.A. Wells* [Sunesis Pharm]

Curr. Opi. Str. Biol. **31**, 706-715 (2005)

New allosteric sites in enzymes were discovered both incidentally and by directed means and their mechanisms investigated. Structurally well-characterized examples yielded trends for binding modes and mechanisms of inhibition.

Structure-based discovery of human L-xylulose reductase inhibitors from database screening and molecular docking.

V. Carbone, S. Ishikura, A. Hara,
and O. El-Kabbani* [Monash U]

Bioorg. Med. Chem. **13**, 301-312 (2005)

DOCK is used to analyse the 249,071 compounds of the database and retrieved these compounds with high predicted affinity for L-xylulose reductase (XR). To optimise the interaction between the inhibitor and the holoenzyme, the GRID program was used to design de novo compounds based on the inhibitor benzoic acid. The resultant compounds produce inhibitors with improved specificity for XR.

A combined QM/MM approach to protein-ligand interactions: Polarization effects of the HIV-1 protease on selected high affinity inhibitors.

C.. Hensen, J.C. Hermann, K. Nam, S. Ma,
J. Gao* [U Minnesota], and H.-D. Höltje* [Henrich-Heine U]

J. Med. Chem. **47,** 6673–6680 (2004)

A QM/MM simulation of HIV-1 protease reveals that polarization contributes up to one-third of the electrostatic energy, and thus is important to explicitly treat polarization when analyzing the protease inhibitors.

Computational studies and peptidomimetic design for the human p53-MDM2 complex

H. Zhong and H.A. Carlson* [U Michigan]

Proteins **58**, 222-234 (2005)

Extensive GBSA free energy calculations for the binding to MDM2 of p53, a β-peptide p53 mimetic, a different class of MDM2 inhibitors called nutlins, and many alanine-scanning mutants, agree well with a variety of experimental binding data, and help explain observed differences.

Ligand Binding (cont'd)

Receptor rigidity and ligand mobility in trypsin-ligand complexes

O. Guvench, D.J. Price, and C.L. Brooks, 3rd* [TSRI]

Proteins **58**, 407-417 (2005)

Thorough simulation and analysis of Bovine Trypsin reveals no differences in sidechain mobility from ligand binding, and several distinct and significant ligand-binding orientations not seen directly in crystal structures. Re-evaluation of the electron densities indicates some alternative explanations not consistent with the published crystal structure atomic coordinates.

Theoretical investigations of prostatic acid phosphatase

S. Sharma, P. Pirila, H. Kaija, K. Porvari, P. Vihko, and A.H. Juffer* [U Oulu]

Proteins **58**, 295-308 (2005)

Docking, incremental growth with MD simulations and minimization, and affinity prediction by ICM from mimized MD frames and by LIE, including various active site protonation states, is performed on EGFR and ErbB-2 peptides to PAP. The importance of protonation states, ways to predict these a priori, and a possible of PAP in growth factor receptor regulation are discussed.

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Homology modeling, force field design, and free energy simulation studies to optimize the activities of histone deacetylase inhibitors

H. Park and S. Lee * [Seoul U]

J Comput Aided Mol Des **18**, 375-388 (2004)

Zinc and histone deacetylase inhibitor forcefield parameters for Amber are assigned using standard protocols, and used for FEP calculations of relative binding affinities which are explained qualitatively. De-solvation effects are found to be crucial, and implications for inhibitor design and optimization are discussed.

A free energy calculation study of the effect of HF substitution on binding affinity in ligand-antibody interactions.

M. Saito* [Hirosaki U], I. Okazaki, M. Oda, and I. Fujii

J. Comput. Chem. **26,** 272-282 (2005)

A trifluoro-acetyl analog of chloramphenicol phosphonate binds more tightly to catalytic antibody 6D9 than the trihydro version because the fluorinated ligand has higher hydration energy due to unfavorable interactions of the fluorines with the water.

Enzyme Catalysis

Structural bases of hydrogen tunneling in enzymes: progress and puzzles.

Z.X. Liang and J.P. Klinman* [U Calif Berkely]

Curr. Opi. Str. Biol. **31**, 648-655 (2005)

Soybean lipoxygenase-1, thermophilic alcohol dehydrogenase and dihydrofolate reductase are considered to study the enzyme catalysis involving proton, hydride or hydrogen atom transfer reactions. Special attention is afforded on how the protein dynamics modulate hydrogen-tunneling probability and whether the tunneling process contributes to the catalytic power of enzymes.

Enzyme Catalysis (cont'd)

Structure and dynamics of *Candida rugosa* lipase: The role of organic solvent.

B.A. Tejo, A.B. Salleh and J. Pleiss* [U Stuttgart]
J. Mol. Mod. **10,** 358-366 (2004)

MD simulations are used to study the effect of organic solvent on the structure and dynamics of *Candida rugosa* lipase in water and in carbon tetrachloride. Solvent changed the dynamics of the lid, a mobile element involved in activation of the lipase, which fluctuated as a rigid body about its average position. Organic solvents stabilize the lid but render the side chains in the hydrophobic substrate-binding site more mobile.

Cyclic sulfamide HIV-1 protease inhibitors, with sidechains spanning from P2/P2′ to P1/P1′

A. Ax, W. Schaal, L. Vrang, B. Samuelsson, A. Hallberg, and A .Karlén* [Uppsala U]

Bioorg. Med. Chem. **14**, 755-764 (2005)

Molecular modeling suggested that the design of inhibitors reaching between the S1/S1′ and S2/S2′ binding sites is achieved with appropriate *ortho*-substitution of the P2/P2′ benzyl groups in cyclic sulfamide inhibitors.

Substrate hydroxylation in methane monooxygenase: quantitative modeling via mixed quantum mechanics / molecular mechanics techniques.

B.F. Gherman, S.J. Lippard* [MIT],
and R.A. Friesner* [Columbia U]

J. Amer. Chem. Soc. 127, 1025-1037 (2005)

B3LYP DFT / OPLS-AA calculations with the Qsite program coupling Jaguar and IMPACT in investigate atoms within 35 Å of the active site of one of the monomers of methane monooxygenase. Results are in agreement with experiment regarding the observed kinetic isotope effects variously substituted methane hydroxylation. The calculations also point out deficiencies in the free energy of binding estimates likely related to sampling or inaccurate harmonic estimates of entropy.

Oxidation of methionine residues in aqueous solutions: Free methionine and methionine in granulocyte colony-stimulating factor.

J.-W. Chu, B.R. Brooks, and B.L. Trout* [MIT]

J. Amer. Chem. Soc. **126**, 16601-16607 (2004)

QM/MM, constrained MD and committor probability calculations are applied to compute free energy barriers for free and protein-constrained methionine. The calculations show a strong effect of the protein environment (granulocyte colony stimulating factor) on the oxidation of methionine.

Protein-Protein Interactions

Sampling the self-assembly pathways of KFFE hexamers.

G. Wei, N. Mousseau* [U Montreal], and P. Derreumaux

Biophys. J. **87,** 3648-3656 (2004)

MC simulations of a box of 6 KFFE peptides show they aggregate in sheet and barrel-like curved structures. The force field is simple, with side chains being represented by single atoms. Solvation seems to be implicit.

Protein-Protein Interactions (cont'd)

Oligomerization of amyloid Aβ_{16-22} peptides using hydrogen bonds and hydrophobicity forces.

G. Favrin, A. Irbäck* [Lund U], and S. Mohanty

Biophys. J. **87,** 3657-3664 (2004)

MC simulations of 1, 3, and 6 peptides in a box with a simplified force field shows that the single 7-mer lacks secondary structure, whereas 3- and 6-peptide systems form β-sheet aggregates.

Kinetics of filament bundling with attractive interactions.

X. Yu* [Washington U] and A.E. Carlsson

Biophys. J. **87,** 3679-3689 (2004)

BD simulations of rigid filaments with simplified interactions and differential translational and rotational diffusion coefficients show that fibers tend to collide repeatedly, align, and then optimize contact area by sliding. Fiber length effects cancel out.

Phase diagrams describing fibrillization by polyalanine peptides.

H.D. Nguyen and C.K. Hall* [N Carolina State U]

Biophys. J. **87,** 4122-4134 (2004)

Amylloid formation was studied using replica exchange MD with a simplified force field (PRIME). Systerms were comprised of 96 Ac-$KA_{14}K$-NH_2 peptides.

Entropy calculation of HIV-1 Env gp120, its receptor CD4, and their complex: An analysis of configurational entropy changes upon complexation.

S.-T.D. Hsu, C. Peter, W.F. van Gunsteren, and A.M.J.J. Bonvin* [Utrecht U]

Biophys. J. **88,** 15-24 (2005)

Sufficient conformational sampling was achieved in 10 ns of simulation to adequately predict the large entropy-enthalpy compensation seen when gp120 binds to the membrane protein, CD4. Orientational entropy was computed with a heuristic formula based on the covariance matrix of atom-position fluctuations.

Anchor profiles of HLA-specific peptides: analysis by a novel affinity scoring method and experimental validation

J. Desmet* [AlgoNomics], G. Meersseman, N. Boutonnet, J. Pletinckx, K. De Clercq, M. Debulpaep, T. Braeckman, and I. Lasters

Proteins **58***,* 53-69 (2005)

A novel scoring function for protein-peptide interactions is presented, based on CHARMM, and tested on HLA-A1, -A2, -A24, and -B7 receptors. Implications for specificity of binding profiles are discussed.

The impact of protein flexibility on protein-protein docking

L.P. Ehrlich, M. Nilges, and R.C. Wade* [EML Res]

Proteins **58***,* 126-133 (2005)

From testing of schemes for local protein flexibility with torsion angle dynamics simulation in protein-protein docking on barnase and barnstar, and comparing with rigid docking, it is concluded that sidechain and backbone flexibility must be treated properly and simultaneously in order for the proper contacts to form

Protein-Protein Interactions (cont'd)

Optimal docking area: a new method for predicting protein-protein interaction sites

J. Fernandez-Recio, M. Totrov, C. Skorodumov, and R. Abagyan* [TSRI]

Proteins **58**, 134-143 (2005)

Atomic solvation parameters for protein-protein docking are used to identify surface patches on proteins that are favorable to burial, for about 50% of 66 complexes no interface could be predicted, and 80% of predicted interfaces were correct. The better prediction of X-ray versus NMR complexes is discussed, as are possible applications of the method in general protein structure analysis.

Extent of protein-protein interactions and quasi-equivalence in viral capsids

C.M. Shepherd and V.S. Reddy* [TSRI]

Proteins **58**, 472-477 (2005)

The fraction of buried protein surface in a viral capsid is determined from ~74 high-resolution X-ray structures. Capsids of different symmetry show different or no dependence of this fraction on the subunit weight and capsid size, indicating differences in interaction strength needed. Implications for the evolutionary design of capsids are discussed.

Membrane Proteins and Lipid-Peptide Interactions

Water and ion permeation in bAQP1 and GlpF channels: A kinetic Monte Carlo study.

G.V. Miloshevsky and P.C. Jordan* [Brandeis U]

Biophys. J. **87,** 3690-3702 (2004)

MC with explicit waters and rigid channels shows that selectivity is primarily electrostatic, with large electrostatic energy barriers to anions and cations in each end of the pore. A single-file bipolar water column interrupted with a multiply coordinated water molecule in the selectivity filter, forms in bAQP1 and may contribute to proton block, but the GlpF pore is too large for this mechanism.

Nucleotide-dependent conformational changes in HisP: Molecular dynamics simulations of an ABC transporter nucleotide-binding domain.

J.D. Campbell, S.S. Deol, F. M. Ashcroft, I.D. Kerr, and M.S.P. Sansom* [U Oxford]

Biophys. J. **87,** 3703-3715 (2004)

Modeling of the NBD from a bacterial ATP-binding cassette histidine transporter shows that ATP-Mg binding results in rotation of three α-helices in the subdomain. These are expected to cause the conformational changes needed for transport.

Relating microscopic charge movement to macroscopic currents: The Ramo-Shockley theorem applied to ion channels.

W. Nonner* [U Miami], A. Peyser, D. Gillespie, and B. Eisenberg

Biophys. J. **87,** 3716-3722 (2004)

The Ramo-Shockley theorem, a generalization of Kirchoff's current law that takes displacement currents in the voltage-clamp electrodes into account, allows the computation of gating currents for voltage-gated ion channels in cell membranes for each time step of an MD simulation.

Membrane Proteins and Lipid-Peptide Interactions (cont'd)

Lipid-protein interactions of integral membrane proteins: A comparative simulation study.

S.S. Deol, P.J. Bond, C. Domene, and M.S.P. Sansom* [U Oxford]

Biophys. J. **87,** 3737-3749 (2004)

Boundary lipids around KcsA or OmpA diffuse at about half the bulk rate due to interactions from Trp, Tyr, Arg, or Lys in a 1 nm band on each side of the proteins. The basic residues interact strongly with lipid phosphates. Specific and non-specific interactions typically have durations of 1-5 ns.

Plasticity of Influenza haemagglutinin fusion peptides and their interaction with lipid bilayers.

L. Vaccaro, K.J. Cross, J. Kleinjung, S.K. Straus, D.J. Thomas, S.A. Wharton, J.J. Skehel, and F. Fraternali* [NIMR]

Biophys. J. **88,** 25-36 (2005)

The first 20 residues of hemaglutinnin insert into a lipid membrane at an angle of 30°, disordering the lipid molecules according to MD simulations, explaining fusogenicity. Mutations that remove fusogenicity cause the peptide to lie on the bilayer surface instead. Homologous sequences are found in prion, porin, and amyloid αβ, consistent with environment-dependent functional plasticity.

Molecular dynamics simulation of transmembrane polypeptide orientational fluctuations.

D.J. Goodyear, S. Sharpe, C.W.M. Grant, and M.R. Morrow* [Memorial U Newfoundland]

Biophys. J. **88,** 105-117 (2005)

MD with acetyl-KK-$(LA)_{11}$-KK-amide in POPC confirmed the NMR observation that the helix tilt and azimuthal angle about the helix axis remain constant while the peptide precesses in the membrane.

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Modeling P-Loops domain of sodium channel: Homology with potassium channels and interaction with ligands.

D.B. Tikhonov and B.S. Zhorov* [McMaster U]

Biophys. J. **88,** 184-197 (2005)

The P-loops of the sodium channel were modeled about the known saxitoxin and tetrodotoxin complexation determinants in the context of the MthK pore helix structure. The result turned out to be more similar to potassium channel structure than expected, while successfully explaining known μ-conotoxin binding contacts, tetramethylammonium permeation in the DEAA but not the AAAA mutants of the DEKA selectivity filter, and Na:Ca selectivity in the DEKA sodium channel and the EEEE calcium channel homolog.

Molecular dynamics simulations of discoidal bilayers assembled from truncated human lipoproteins.

A.Y. Shih, I.G. Denisov, J.C. Phillips, S.G. Sligar, and K. Schulten* [U Illinois Urbana-Champaign]

Biophys. J. **88,** 548-556 (2005)

Nanodiscs can be formed with polymers of the high density lipoprotein component Apo-A1. Comparison of computational and experimental results suggests that the first 17 residues do not participate in the protein scaffold. The lipid bilayer within the scaffolding is planar and can nicely accommodate bacteriorhodopsin.

Membrane Proteins and Lipid-Peptide Interactions (cont'd)

Conformational dynamics of the nicotinic acetylcholine receptor channel: A 35-ns molecular dynamics simulation study.

Y. Xu, F.J. Barrantes, X. Luo, K. Chen, J. Shen*
[Chinese Acad Sci], and H. Jiang* [Chinese Acad Sci]

J. Amer. Chem. Soc. **127**, 1291-1299 (2005)

MD simulation with the GROMOS87 force field (an interesting choice) and a PME treatment investigate the nicotinic ACh receptor in a full DPPC bilayer environment. The protein simulated includes the entire membrane spanning region including the central ion channel pore. A closed to open shift was observed (despite the lack of activation) and both symmetric and asymmetric motions of the helices illuminated.

Molecular dynamics simulations of GlpF in a micelle vs. in a bilayer: Conformational dynamics of a membrane protein as a function of environment.

G. Patargias, P.J. Bond, S.S. Deol,
and M.S.P. Sansom* [U Oxford]

J. Phys. Chem. B **109**, 575-582 (2005)

MD simulation look at the differences in structure and dynamics of the a-helical membrane protein GlpF in octyl glucoside micelles compared to DMPC bilayers.

Protein-Nucleic Acid Interactions

Role of the linker domain and the 203–214 N-terminal residues in the human topoisomerase I DNA complex dynamics.

G. Chillemi, M. Redinbo, A. Bruselles,
and A. Desideri* [U Rome Tor Vergata]

Biophys. J. **87**, 4087-4097 (2004)

If the N-terminus and linker domains are removed from topoisomerase, the dynamics of the crystal structure are more extensive and many components of a complex hydrogen-bonded network in the active site important for relaxing DNA are lost. The network involves many important water molecules, including one that is poised to accept a proton from a catalytic Tyr side-chain.

Nucleic Acids

Molecular dynamics simulations of the 136 unique tetranucleotide sequences of DNA oligonucleotides. I. Research design and results on d(C_pG) steps.

D.L. Beveridge* [Wesleyan U], G. Barreiro, K.S. Byun,
D.A. Case, T.E. Cheatham, III, S.B. Dixit, E. Giudice,
F. Lankas, R. Lavery, J.H. Maddocks, R. Osman, E. Seibert,
H. Sklenar, G. Stoll, K.M. Thayer, P. Varnai,
and M.A. Young

Biophys. J. **87,** 3799-3813 (2004)

This is the first report from a large-scale simulation of 15-pair simulations for each of the possible tetranucleotide sequences. The AMBER force field with parm94 is being used.

The triplex-hairpin transition in cytosine-rich DNA.

A.S. Petrov, G. Lamm, and G.R. Pack* [U Louisville]

Biophys. J. **87,** 3954-3973 (2004)

The self-complementary single-stranded 30-mer, ***d***(TC*TTC*C*TTTTCCTTCTC*CCGAGAAGGTTTT), folds back on itself twice when the C* are protonated allowing Hoogsteen triple helix hydrogen bonds with the guanine of a GC pair. MD with PB-dependent titration of the C* show that formation of the triple helix configuration is indeed dependent on the protonation of the cytosines.

Nucleic Acids (cont'd)

Monte Carlo simulation for single RNA unfolding by force.

F. Liu* [Tsinghua U] and Z. Ou-Yang

Biophys. J. **88,** 76-84 (2005)

Steered MC simulations were used to simulate the force-extension curves for P5ab, P5abcA, and P5abc molecules using a simple force field. Length-tension curves, folding rate constants, and end-end distance distributions are consistent with experimental results.

Loop-length-dependent folding of G-quadruplexes.

P. Hazel, J. Huppert, S. Balasubramanian, and S. Neidle* [U London]

J. Amer. Chem. Soc. **126**, 16405-16415 (2004)

CD, UV melting data and MD simulation combine to give insight into G-quadruplex formation.

Lipids and Surfactants

Molecular view of hexagonal phase formation in phospholipid membranes.

S.-J. Marrink* [U Groningen] and A.E. Mark

Biophys. J. **87,** 3894-3900 (2004)

A course-grained model was used to simulate the transition, via stalk formation, between the multilammelar bilayer stage and inverted hexagonal phase lipid. Stalk elongation at a rate of 1 Å/ns leads eventually to rhombohedral phase.

Molecular dynamics simulation of a rising bubble.

M. Matsumoto*[Kyoto U] and T. Matsuura

Mol. Sim. **30**, 853-859 (2004)

MD simulations are used to investigate the effects of surface adsorption on a bubble moving in a uniform force field. No flow is observed on the bubble surface when sufficient amount of surfactants are adsorbed on the bubble surface, and the terminal velocity drastically decreases.

MD simulations of spontaneous membrane protein/detergent micelle formation.

P.J. Bond, J.M. Cuthbertson, S.S. Deol, and M.S.P. Sansom* [Oxford U]

J. Amer. Chem. Soc. **126**, 15948-15949 (2004)

Two 50-ns MD simulations display spontaneous association of a protein/detergent micelle of DPC lipids with OmpA and GpA membrane proteins.

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Molecular modeling and simulations of AOT-water reverse micelles in isooctane: Structural and dynamic properties.

S. Abel, F. Sterpone, S. Bandyopadhyay, and M. Marchi* [CNRS]

J. Phys. Chem. B **108**, 19458-19466 (2004)

The reverse micelle composed of water and sodium di-2-ethylhexylsolfoccinate (AOT) in isooctane, corresponding to the L2 ternary phase, is investigated in MD simulation. Ion solvation is facilitated in larger micelles, as well as water diffusion (which is less than bulk in smaller micelles).

Molecular dynamics simulation of a GM3 ganglioside bilayer.

M. Sega, R. Vallauri* [U Trento], P. Brocca, and S. Melchionna

J. Phys. Chem. B **108**, 20322-20330 (2004)

The first simulations of the GM3 bilayer (containing glucose, galatose and sialic acid as the headgroups and sphingoside as the fatty acid) in the context of the GROMOS87 force field are described. It is claimed that full equilibration is attained by 30 ns of simulation (although the energy of the system seems to continue to be relaxing at ~45 ns).

Impact of cholesterol on voids in phospholipid membranes.

E. Falck* [Helsinki U Tech], M. Patra, M. Karttunen, M.T. Hyvönen, and I. Vattulainen

J. Chem. Phys. **26,** 12676-12689 (2004)

Voids in DPPC bilayers are reduced with the addition of cholesterol (up to 30% mole fraction) according to MD simulations. Residual voids are oriented along the normal and are located near the cholesterol molecules.

Simulation studies of pore and domain formation in a phospholipid monolayer.

V. Knecht* [U Groningen], M. Müller, M. Bonn, S.-J. Marrink, and A.E. Mark

J. Chem. Phys. **122,** 02470401-02470409 (2005)

MD simulations of a DPPC monolayer on a water surface show that when stretched to 1.0 nm2/headgroup pores form and order is restored to the tails, consistent with vibrational sum-frequency generation spectra that show a sharp transition at 1.1 nm2. Between 0.6 and 1.0 nm2 liquid ordered and disordered states coexist.

1.3. Polymers

Polymer nanodroplets forming liquid bridges in chemically structured slit pores: A computer simulation.

J. Yaneva* [Bulgarian Acad Sci], A. Milchev, and K. Binder

J. Chem. Phys. **26,** 12632-12639 (2004)

The dynamics and forces of liquid polymer droplets on lyophilic spots in a lyophobic wall, and of pairs of droplets on opposite walls as a function of wall separation were used to estimate droplet aggregation, bridge formation, and gluing forces.

1.4. Surfaces, Catalysts, and Material Subjects

Dynamics of driven systems from Newtonian to athermal limits.

D.J. Lacks* [Case Western Reserve U]

Mol. Sim. **30**, 831-834 (2004)

NMED simulations are applied to investigate the dynamics and properties of driven flowing systems. The aim of this work is to link the properties of flowing thermal system like liquids and colloids to flowing athermal systems like foams and granular materials.

Contact forces at the sliding interface: Mixed versus pure model alkane monolayers.

P.T. Mikulski* [US Naval Acad], G. Gao, G.M. Chateauneuf, and J.A. Harrison

J. Chem. Phys. **122,** 02470101-02470109 (2005)

Tightly packed 14-carbon alkane chains give less resistance to a simulated AFM tip than do random mixtures of 12- and 16-carbon chains. Force distributions are analyzed in detail. Probe motions produce a cant; resistance with the cant is lower than perpendicular to the cant.

2. METHODOLOGY

Bioinformatics

MSDsite: a database search and retrieval system for the analysis and viewing of bound ligands and active sites

A. Golovin, D. Dimitropoulos, T. Oldfield, A. Rachedi, and K. Henrick* [Welcome Trust Genome Campus]

Proteins **58,** 190-199 (2005)

Ligand active site interactions (from PDB structures) were classified in ionic, Van der Waals, rings, planar groups, metal coordination and sequence patterns, and stored in a database server. A graphical search and retrieval option is developed.

Quantitative Structure-Activity Relations

An automated PLS search for biologically relevant QSAR descriptors

M. Olah, C. Bologa, and T.I. Oprea* [U New Mexico]

J Comput Aided Mol Des **18,** 437-450 (2004)

The relevance of various 2D, MDL320, SMARTS Q504 and F504 descriptors is evaluated on 1600 N>=25 series from the WOMBAT database. The SMARTS-Q504 perform best, the 2D descriptors worst. Several of the most relevant descriptors are discussed in detail.

Variable selection and model validation of 2D and 3D molecular descriptors

A. Nicholls* [OpenEye], N.E. MacCuish, and J.D. MacCuish

J Comput Aided Mol Des **18,** 451-474 (2004)

A extensive and thorough evaluation of a (3D) shape and electrostatics comparison method is presented, used as 'Tanimoto's' in a 3D QSAR method, and validated against X-ray structures of Cox2, progesterone and calcium ion channel protein-ligand complexes.

Genetic algorithms and self-organizing maps: a powerful combination for modeling complex QSAR and QSPR problems

E. Bayram, P. Santago II, R. Harris, Y.D. Xiao, A.J. Clauset, and J.D. Schmitt* [Targacept]

J Comput Aided Mol Des **18,** 483-494 (2004)

GA and SOM combined are evaluated for automated QSAR derivation and, although GA-SOM parameters were not yet optimized, are found to outperform standard PLS methods.

Quantitative Structure-Activity Relationships

Descriptors you can count on? Normalized and filtered pharmacophore descriptors for virtual screening

A.C. Good* [Bristol-Myers Squibb], S.J. Cho, and J.S. Mason

J Comput Aided Mol Des **18**, 523-528 (2004)

An evaluation of the noise-eliminating capacity of filtered, normalized and binary descriptors in QSAR is presented. Normalization is found to give the highest increase in enrichment, with some additional gain by filtering, and binary descriptors perform much worse.

Statistical variation in progressive scrambling

R.D. Clark* [Tripos] and P.C. Fox

J Comput Aided Mol Des **18**, 563-576 (2004)

!

A thorough statistical analysis of methods for QSAR model predictivity and robustness evaluation is presented. The commonly used cross-validation (leave one or some out) are shown to be ill suited for (semi-)redundant datasets, which is common in (chemical) databases. Advantages and limitations of a 'progressive scrambling' method are investigated and discussed in depth.

Conformational Search and Analysis

Conformational sampling of the botulinum neurotoxin serotype A light chain: Implications for inhibitor binding

J.C. Burnett, J.J. Schmidt, C.F. McGrath, T.L. Nguyen, A.R. Hermone, G.P. Rekha, J.L. Vennerstrom, K. Krishna, D.W. Zaharevitz, R. Gussio, and S. Bavari* [NCI Frederick]

Bioorg. Med. Chem. **13**, 333-341 (2005)

3BTA and 1E1H structures were analyzed to study the influence of the dynamic movement of amino acid residues in and surrounding the substrate binding-cleft of the BoNT/A LC inhibitor binding modes. Conformational flexibility was observed in surface loops bordering the substrate binding clefts in both structures. The results aided in the subsequent identification of more potent inhibitors taking advantage of new binding contacts.

Use of block Hessians for the optimization of molecular geometries.

J. Pu and D.G. Truhlar* [U Minnesota]

J. Chem. Theory Comput. **1,** 54-60 (2005)

To speed up geometry optimization, a block Hessian approach is developed where a small critical block is computed at a high level, and less critical blocks are computed at a lower level.

Potentials and Parameters

DommiMOE: An implementation of ligand field molecular mechanics in the molecular operating environment.

R.J. Deeth* [U Warwick], N. Fey, and B. Williams-Hubbard

J. Comput. Chem. **26,** 123-130 (2005)

MOE

Automatically determine new force field parameters for novel ligands. The software was implemented in MOE using MOE's scientific vector language.

Multibaric-multithermal ensemble simulation for simple liquids.

H. Okumura* [Inst Mol Sci] and Y. Okamoto

Mol. Sim. **30**, 847-852 (2004)

A generalized isobaric-isothermal ensemble Monte Carlo algorithm, referred to as the multibaric-multithermal algorithm is presented. The effectiveness of this algorithm is applied to Lennard-Jones 12-6 potential system.

Potentials and Parameters (cont'd)

Interatomic potentials for simulating MnO_2 polymorphs.

S.D. Fleming* [Curtin U Tech], J.R. Morton, A.L. Rohl, and C.B. Ward

Mol. Sim. **31**, 25-32 (2005)

The results suggested that tunnels larger than 2×3 are not stable without the presence of additional species within them. The stabilities of the polymorphs were calculated and it was found that the spinel-based structure is less stable than the tunnel structures.

Parameterization of reversible digitally filtered molecular dynamics simulations.

A.P. Wiley, M.T. Swain, S.C. Phillips, J.W. Essex* [U Southampton], and C.M. Edge

J. Chem. Theory Comput. **1,** 24-35 (2005)

"Reversible Digitally Filtered Molecular Dynamics (RDFMD) is a method of amplifying or suppressing motions in a MD simulation through the application of a digital filter to the simulation velocities." A new parameter set for RDFMD is found through systematic analysis, and then applied to generate a progressive trajectory with maximal conformational change for a pentapeptide and for the DHFR protein.

!

Benchmarking the conductor-like polarizable continuum model (CPCM) for aqueous solvation free energies of neutral and ionic organic molecules.

Y. Takano and K.N. Houk* [UCLA]

J. Chem. Theory Comput. **1,** 70-77 (2005)

CPCM approaches are benchmarked against each other as well as other solvation models in their ability to reproduce experimental solvation energies for 70 different neutral and ionic organic species. The best results are seen using CPCM with UAKS cavities.

!

Determination of electrostatic parameters for a polarizable force field based on the classical drude oscillator.

V.M. Anisimov, G. Lamoureux, I.V. Vorobyov, N. Huang, B. Roux, and A.D. MacKerell, Jr.* [U Maryland]

J. Chem. Theory Comput. **1,** 153-168 (2005)

Restrained ESP charges and perturbed ESP maps are used to derive parameters for a force field derived from CHARMM27 that explicitly accounts for many-body induced polarization effects using a classical Drude oscillator model. The parameterized polarizable force field gives reasonable results for a DNA octamer in a box of water with sodium counterions.

!

Trimer based polarization as a multibody molecular model. Application to hydrogen fluoride.

S.J. Wierzchowski and D.A. Kofke* [SUNY Buffalo]

J. Amer. Chem. Soc. **127**, 690-698 (2005)

A truly 3-body (over all timers within a given cutoff) polarization potential is described in the context of Monte Carlo simulation. HF is a simple model that has previously proved difficult.

!

Development of a multipoint model for sulfur in proteins: A new parametrization scheme to reproduce high-level ab initio interaction energies.

F. Wennmohs and M. Schindler* [Bayer CropScience AG]

J. Comput.Chem. **26,** 282-293 (2005)

Weak hydrogen bonds to methionine sulfur require a multipoint potential for accurate representation. A new parameterization was incorporated into GROMACS and tested favorably with two ligand-protein binding cases.

Potentials and Parameters (cont'd)

Monte Carlo versus molecular dynamics simulations in heterogeneous systems: An application to the n-pentane liquid-vapor interface.

F. Goujon* [U Blaise Pascal], P. Malfreyt, J.-M. Simon, A. Boutin, B. Rousseau, and A.H. Fuchs

J. Chem. Phys. **26,** 12559-12571 (2004)

Nonbonded cutoffs distort interfacial structures. MC and MD give similar results provided that the nonbonded rolloff function produces the same first and second derivative for the potential, but when this requirement is imposed, the original parameters used in MD simulations of homogenous solutions are not accurate.

Coulomb potentials in two and three dimensions under periodic boundary conditions.

S. Tyagi* [U Pittsburgh]

J. Chem. Phys. **122,** 01410101-01410112 (2005)

Potentials for homogeneous and slab geometries generalized from Sperb's work [R. Sperb, Mol. Simulation 22, 199 (1999)] converge rapidly in all areas

A nonadditive methanol force field: Bulk liquid and liquid-vapor interfacial properties via molecular dynamics simulations using a fluctuating charge model.

S. Patel* [Scripps] and C.L. Brooks III

J. Chem. Phys. **122,** 02450801-02450810 (2005)

Fluctuating charge methanol does as well or better than fixed charge simulations, and reproduces DFT MD coordination number prediction of 2. Liquid density, enthalpy of vaporization, surface tension and triple point temperature and density were all used in the comparisons.

Gaussian split Ewald: A fast Ewald mesh method for molecular simulation.

Y. Shan* [DE Shaw R&D], J.L. Klepeis, M.P. Eastwood, R.O. Dror, and D.E. Shaw

J. Chem. Phys. **122,** 05410101-05410113 (2005)

Gaussian split Ewald can be combined with k-space Ewald in a Poisson solver to optimize accuracy and speed for biomolecular simulations. The method performs comparably with smooth particle-mesh Ewald.

Solvation Energy

Incorporating the effect of ionic strength in free energy calculations using explicit ions.

S. Donnini, A.E. Mark, A.H. Juffer, and A. Villa* [U Groningen]

J. Comput. Chem. **26,** 115-122 (2005)

How much difference does ionic strength make for ligand binding? Ligands with strong partial charges in the docking region can have significantly reduced affinity, but it is difficult to get enough sampling to check low ionic strength. Better to use high ionic strength or no ions at all.

New Born radii deriving method for generalized Born model.

W. Zhang, T. Hou, and X. Xu* [Peking U]

J. Chem. Inf. Model. **45,** 88-93 (2005)

A method for calculating Born radii based on atom types defined by SMARTS queries is fast compared to integral method approaches. A docking scoring application suggests that this new approach provides a good approximation of PB results.

Solvation Potential (cont'd)

Rapid estimation of solvation energy for simulations of protein-protein association.

D.S. Cerutti* [UC San Diego], L.F. Ten Eyck, and J.A. McCammon

J. Chem. Theory Comput. **1,** 143-152 (2005)

A new empirically fitted PBSA approximation scheme based on a distance-dependent dielectric is useful in scoring of protein-protein docking poses.

Molecular Dynamics

Superposition state molecular dynamics.

A. Venkatnathan and G.A. Voth* [U Utah]

J. Chem. Theory Comput. **1,** 36-40 (2005)

A new method, called superposition state molecular dynamics (SMMD), is a low cost computational method that can be used to ergodically sample rough potential energy surfaces. SSMD is shown to be successful in a case where standard canonical MD and a NHC (Nose-Hoover Chain) fail to sample ergodically

OOPSE: An object-oriented parallel simulation engine for molecular dynamics.

M.A. Meineke, C.F. Vardeman II, T. Lin, C.J. Fennell, and J.D. Gezelter* [U Notre Dame]

J. Comput. Chem. **26,** 252-271 (2005)

OOPSE is designed to efficiently simulate orientation dependent atoms (point dipoles and metal ions) and is more effective than previous quaternion simulation programs.

Functionally relevant protein motions: Extracting basin-specific collective coordinates from molecular dynamics trajectories.

P.W. Pan* [Brock U], R.J. Dickson, H.L. Gordon, S.M. Rothstein, and S. Tanaka

J. Chem. Phys. **122**, 03490401-03490410 (2005)

Histogram filtering of inter-Ca distances is used to identify collective coordinates for different conformations. Secondary structures moving as a unit are readily identified this way as well as mobile functional regions.

QM/MM

Theoretical study of the monomer reaction mechanism on Phillips CrO_x/SiO_2 catalyst using density functional theory (DFT) and paired interacting orbitals (PIO) methods.

B. Liu*[AIST], Y. Fang, and M. Terano

Mol. Sim. **30**, 963-971 (2004)

Both DFT and paired interacting orbital (PIO) results showed that GO-2 orientation is the most preferential orientation for the reaction between ethylene monomers and monochromate species.

QM/MM (cont'd)

An efficient linear-scaling ewald method for long-range electrostatic interactions in combined QM/MM calculations.

K. Nam, J. Gao, and D.M. York* [U Minnesota]

J. Chem. Theory Comput. **1,** 2-13 (2005)

The Ewald sum method is implemented for QM/MM simulations using CHARMM and MNDO97, and the implementation is demonstrated in a simulation of ion association and dissociation in phosphoryl transfer.

Variational electrostatic projection (VEP) methods for efficient modeling of the macromolecular electrostatic and solvation environment in activated dynamics simulations.

B.A. Gregersen, and D.M. York* [U Minnesota]

J. Phys. Chem. B **109**, 536-556 (2005)

The variational electrostatic projection method is described in a QM/MM context and applied to two catalytic RNA systems. The method utilizes an expansion in Gaussian surface elements and proves to be promising.

Microscopic and macroscopic polarization within a combined quantum mechanics and molecular mechanics model.

L. Jensen* [Rijksuniversiteit Groningen], M. Swart, and P.Th. van Duijnen

J. Chem. Phys. **122,** 03410301-03410314 (2005)

"By separating the discrete local field into two distinct contributions," the authors "define two different microscopic properties, the so-called solute and effective properties." Refractive index and third harmonic generation are well predicted by simulations with acetonitrile and water.

Comparative or Homology Modeling

Relationship between multiple sequence alignments and quality of protein comparative models

D. Cozzetto and A. Tramontano* [U "La Sapienza"]

Proteins **58***,* 151-157 (2005)

A thorough analysis of homology models compared between CASP4 (2001) and CASP5 (2003) targets, shows the increased number of homologous sequences available for the multiple sequence alignments as the main factor for improved quality of the final structural models, and not improved modeling methodology.

Peptide Conformational Analysis

Monte Carlo simulations of polyalanine using a reduced model and statistics-based interaction potentials.

A.E. van Giessen* [Boston U] and J.E. Straub

J. Chem. Phys. **122,** 02490401-02490409 (2005)

A course-grained structural model consisting of two sites per residue (one for the side chain and one for backbone hydrogen-bonding) performs as well at reproducing the thermodynamics of the coil-helix transition as all-atom and other reduced-atom MC approaches.

Protein Structure Prediction

A method for structural analysis of α-helices of membrane proteins.

P.K. Mohapatra, A. Khamari,
and M.K. Raval* [Govt College, Sundargarh]

J. Mol. Mod. **10**, 393-398 (2004)

The axis of the helix is determined from the local centroids of tetrapeptide units of the helix. This method provides lower and upper cutoff values of the distance between backbone atoms C_i (carbonyl carbon) and N_{i+4} for allocation of a hinge in a helix. The parameters are useful in quantitative descriptions of structural features of membrane proteins.

Predicting absolute contact numbers of native protein structure from amino acid sequence

A.R. Kinjo* [Ntl Inst Gen], K. Horimoto, and K. Nishikawa

Proteins **58***,* 158-165 (2005)

A method for predicting contact number (number of Cβ-Cβ neighbors) from sequence is presented. The use of multiple sequence alignments (MSA) improves accuracy of predictions, but use of MSA's during method training does not. The use of contact number versus ASA in other applications, e.g. fold or structure prediction, is discussed.

Threading or Fold Prediction

Fold recognition by combining sequence profiles derived from evolution and from depth-dependent structural alignment of fragments

H. Zhou and Y. Zhou* [U New York Buffalo]

Proteins **58***,* 321-328 (2005)

A fold prediction method is presented that is based mainly on sequence profiles, and shown to outperform other single-method severs and compete with the best consensus servers on accuracy and sensitivity.

How effective for fold recognition is a potential of mean force that includes relative orientations between contacting residues in proteins?

S. Miyazawa* [Gunma U, Iowa State U] and R.L. Jernigan

J. Chem. Phys. **122,** 02490101- 02490118 (2005)

Native folds can be recognized better by included a statistical potential based on orientations of neighboring residues in proteins. However, to obtain an adequate orientation potential with the limited examples in the PDB, a spherical harmonic expansion of delta functions, each representing on observed example, is utilized.

Protein Folding

Study of the Villin headpiece folding dynamics by combining coarse-grained Monte Carlo evolution and all-atom molecular dynamics

G.M. De Mori, G. Colombo* [Inst Chim Ric Mol Milano],
and C. Micheletti* [SISSA]

Proteins **58***,* 459-471 (2005)

Initial course-grained MC combined with seven subsequent atomic, explicit solvent MD is used to derive insights into the sequence of events in villin headpiece folding. One MD simulation reaches 4 Å deviation from the NMR structure (2.4 in the core). The balance of local-nonlocal interactions is discussed.

Protein Folding (cont'd)

Explicit-chain model of native-state hydrogen exchange: implications for event ordering and cooperativity in protein folding

H. Kaya and H.S. Chan* [U Toronto]

Proteins **58,** 31-44 (2005)

A thorough consideration of cooperativity and multistate thermodynamics, definitions of intermediate states, and shortcomings of the numerous previous model studies, is the basis for a more in-depth understanding of hydrogen-exchange data of proteins. Interestingly, a statistical, not absolute, ordering of late-folding events is observed.

!

Ligand Docking

ProPose: A docking engine based on a fully configurable protein–ligand interaction model.

M.H.J. Seifert* [Am Klopferspitz**]**, F. Schmitt, T. Herz, and B. Kramer
J. Mol. Mod. 10, 342-357 (2004)

ProPose, an advanced incremental construction docking program, implements a fast and fully configurable molecular interaction and scoring model. The integration of pharmacophore-like interaction types into the docking and scoring scheme implemented in ProPose opens new opportunities for efficient, receptor-specific screening protocols.

!

Ph4Dock: Pharmacophore-based protein-ligand docking.

J. Goto, R. Kataoka, and N. Hirayama* [Tokai U]

J. Med. Chem. **47,** 6804 – 6811 (2004)

The Ph4Dock implementation of the docking approach whereby explicit prealigned pharmacophore features from known ligands are used is shown to be rapid and effective when tested using a dataset of 43 co-complex crystal structures.

Method for computing protein binding affinity.

C.F.F. Karney* [Sarnoff Corp], J.E. Ferrara, and S. Brunner

J. Comput. Chem. **26,** 243-251 (2005)

A continuum solvent Monte Carlo algorithm uses a configuration space variable indicating whether a ligand is docked or not for MC moves. Used with known complex structures, it provides a quantitative estimate of ligand docking energy.

Molecular Graphics

Interactive essential dynamics

J. Mongan* [UCSD]

J Comput Aided Mol Des **18***,* 433-436 (2004)

An interactive graphical interface within VMD for Essential Dynamics (or Normal Modes) analysis, projection and filtering of MD simulations is presented. The analysis itself can be performed in VMD, or externally with Amber or Gromacs.

Structure Determination

Refinement of NMR structures using implicit solvent and advanced sampling techniques.

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

J. Amer. Chem. Soc. **126**, 16038-16047 (2004)

Replica-exchange and generalized Born methods combine as a tool for better NMR structure refinement. When the NMR data is limited, implicit solvent and sampling become rather important and could prove useful for early stage fold refinement.

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

Journal of Computational Chemistry 26(2), January 30, 2005

115-122 **Incorporating the effect of ionic strength in free energy calculations using explicit ions.** S. Donnini, A.E. Mark, A.H. Juffer, and A. Villa* [U Groningen]. See **Methodology, Solvation Energy.**

123-130 **DommiMOE: An implementation of ligand field molecular mechanics in the molecular operating environment.** R.J. Deeth* [U Warwick], N. Fey, and B. Williams-Hubbard. See **Methodology, Potentials and Parameters.**

131-141 **Evolutionary method for the assembly of rigid protein fragments.** D. De Sancho, L. Prieto, A.M. Rubio, and A. Rey* [U Complutense]

Crossover between independently evolving substructures can speed the genetic algorithm.

142-144 **MoCalc: A new graphical user interface for molecular calculations.** D.B. Depizzol, M.H.M. Paiva, T.O. Dos Santos, and A.C. Gaudio* [Fed U Espírito Santo]. .

A Visual Basic interface for GAMESS and MOPAC.

145-153 **Reduced-size polarized basis sets for calculations of molecular electric properties. I. The basis set generation.** Z. Benkova, A.J. Sadlej, R.E. Oakes, and S.E.J. Bell* [Queen's U Belfast]

Improved basis sets for polarized molecules are dubbed Z*m*PolX.

154-159 **Reduced-size polarized basis sets for calculations of molecular electric properties. II. Simulation of the Raman spectra.** R.E. Oakes, S.E.J. Bell* [Queen's U Belfast], Z. Benkova, and A.J. Sadlej

Z*m*PolX basis sets are used for calculations of frequencies and intensities in the Raman spectra of large organic molecules. They are very fast and small.

160-168 **A quantum chemical method for rapid optimization of protein structures.** M. Wada and M. Sakurai* [Tokyo Inst Tech]

Optimize the amino acids in their environments independently. Repeat until convergence.

169-174 **Urea: An *ab initio* and force field study of the gas and solid phases.** H. Sun* [Shanghai Jiao Tong U] and P.W.-C. Kung

Urea is nonplanar in the gas phase, but becomes planar in the crystal, according to *ab initio* computations, because the planar phase is more polar and increases electrostatic interactions. A force field for the condensed phase tests out in MD simulations.

175-184 **Newly developed basis sets for density functional calculations.** S. Chiodo, N. Russo* [U della Calabria], and E. Sicilia

Optimized contracted Gaussian basis sets of double-zeta valence polarized (DZVP) quality for first-row transition metals are presented

184-193 **Theoretical study and rate constant calculation for the reactions of SH (SD) with Cl_2, Br_2, and BrCl.** L. Wang, J.-Y. Liu, Z.-S. Li* [Jilin U], and C.-C. Sun

SH + Br_2 and SH + BrCl have negative activation energies and kinetic isotope effects are inverted according to *ab initio* calculations.

194-200 **Charge donation to and dearomatization of benzene attending complexation: DFT estimates of binding energies of TpMXO(L) with benzene, for Tp = hydridotris(pyrazolyl) borate, MXO = MoNO, ReCO, and WNO, and L = ammonia, *N*-methylimidazole, pyridine, phosphine, methyl isocyanide, and carbon monoxide.** W.D. Harman and C. Trindle* [U Virginia]

Complexation of benzene causes dearomatization, with either charge being contributed to benzene (up to 0.5 e) for strong complexation, or taken from benzene for the weakest binding cases.

Journal of Computational Chemistry 26(3), February, 2005

201-213 **Simulations of the active transport of a neutral solute based on a kinase-channel-phosphatase topology.** K. Fiaty, C. Charcosset, B. Perrin, R. Couturier, and B. Maïsterrena* [U Claude Bernard Lyon 1]

Flux equation analysis of transporter function. My cup of tea, but not yours…

214-225 **Registering the Amica electronic structure code in the Extensible Computational Chemistry Environment.** R.J. Gdanitz* [North Carolina A&T State U], G.D. Black, C. S. Lansing, B.J. Palmer, and K.L. Schuchardt

ECCE was incorporated as a graphical user interface for Amica (Atoms & Molecules In Chemical Accuracy).

226-234 **Electronic structure and stability of AlnPn (n = 2-4) clusters.** Y. Qu* [Shandong U] and X. Bian

Cluster stability and dynamics was studied using DFT.

235-242 **Theoretical calculations of homoconjugation equilibrium constants in systems modeling acid-base interactions in side chains of biomolecules using the potential of mean force.** J. Makowska, M. Makowski* [U Gdańsk], A. Liwo, and L. Chmurzyski. See **Applications, Model Systems.**

243-251 **Method for computing protein binding affinity.** C.F.F. Karney* [Sarnoff Corp], J.E. Ferrara, and S. Brunner. See **Methodology, Ligand Docking.**

252-271 **OOPSE: An object-oriented parallel simulation engine for molecular dynamics.** M.A. Meineke, C.F. Vardeman II, T. Lin, C.J. Fennell, and J.D. Gezelter* [U Notre Dame]. See **Methodology, Molecular Dynamics.**

272-282 **A free energy calculation study of the effect of HF substitution on binding affinity in ligand-antibody interactions.** M. Saito* [Hirosaki U], I. Okazaki, M. Oda, and I. Fujii. See **Applications, Ligand Binding.**

283-293 **Development of a multipoint model for sulfur in proteins: A new parametrization scheme to reproduce high-level ab initio interaction energies.** F. Wennmohs and M. Schindler* [Bayer CropScience AG]. See **Methodology, Potentials and Parameters.**

294-303 **Study of electronic spectra of free-base porphin and Mg-porphin: Comprehensive comparison of variety of ab initio, DFT, and semiempirical methods.** J. Šeda, J.V. Burda* [Charles U], and J. Leszczynski

Rydberg molecular orbitals important in determination of the electronic spectra require diffuse-function basis sets.

304-324 **Ab initio crystal structure prediction - I. Rigid molecules.** P.G. Karamertzanis and C.C. Pantelides* [Imperial College London]

Lattice enthalpy is minimized using four stage global minimization with rigid molecules whose parameters are first computed *ab initio*.

Journal of Molecular Modeling 10(5-6), December, 2004

305-316 **Evolutionary trace analysis of ionotropic glutamate receptor sequences and modeling the interactions of agonists with different NMDA receptor subunits.** M.C.Blaise, R.Sowdhamini, M.R. Prasad Rao and N. Pradhan* [NIMHANS]

Evolutionary trace (ET) analysis is carriedout on forty ionotropic glutamate receptor (IGRs) sequences and model the ligand binding core (S1S2) of NMDA receptor subunits using the crystal structure of NR1 subunit ligand binding core.

317-327 **Modeling the E.coli 4-hydroxybenzoic acid oligoprenyltransferase (ubiA transferase) and characterization of potential active sites.** L. Bräuer, W. Brandt and L.A. Wessjohann* [Leibniz Inst Plant Biochem.] See **Applications, Comparative or Homology Modeling**

328-334 **Quantitative structure–activity relationship study on some benzodiazepine derivatives as anti-Alzheimer agents.** B. Debnath, S. Gayen, A. Basu, K. Srikanth and T. Jha* [Jadavpur U] See **Applications, Quantitative Structural Activity Relationship**

335-341 **Determination of fuzy logic membership functions using genetic algorithms: Application to structure–odor modeling.** M. Kissi, M. Ramdani* [Sys Info Rea. Ingen des Sys], M. Tollabi and D. Zakarya

Fuzzy logic has been used as a tool in structure–camphoraceous odor relationships and the genetic algorithms led to 84% correct discrimination between camphor and non-camphor molecules.

342-357 **Pose: A docking engine based on a fully configurable protein–ligand interaction model,** M.H.J. Seifert [Am Klopferspitz], F. Schmitt, T. Herz and B. Kramer. See **Methodology, Ligand Docking**

358-366 **Structure and dynamics of *Candida rugosa* lipase: The role of organic solvent.** B.A. Tejo, A.B. Salleh and J.Pleiss* [U Stuttgart]. **See Applications, Enzyme Catalysis**

367-372 **The HF-SCF energy of HIV-1 MNgp120 V3 hairpin loop conformers**. J.K. Weltman, J.K. Weltman* [Brown U], G. Skowron and G.B. Loriot

Hartree–Fock-self-consistent field method and the GROMOS96 force field is used to determine the energy of the V3-loop-peptide conformers.

373-381 **Molecular dynamics simulations of 14 HIV protease mutants in complexes with indinavir.** X. Chen, I.T. Weber* [Georgia State U] and R.W. Harrison. **See Applications, Medicinal Chemistry and Drug Design**

382-392 **Modeling the helicase domain of Brome mosaic virus 1a replicase**. D. Garriga, J. Dìez and B. Oliva* [U Pompeu Fabra]

The results illustrated that the use of sequence profiles and patterns helps modeling. The helicase mechanism was corroborated by the model and supports the hypothesis that BMV 1a should have helicase activity.

393-398 **A method for structural analysis of α-helices of membrane proteins.** P.K. Mohapatra, A. Khamari, and M.K. Raval* [Govt College, Sundargarh]. **See Methodology, Protein Structure Prediction.**

399-407 **Predicting anti-HIV activity of 2,3-diaryl-1,3-thiazolidin-4-ones: Computational approach using reformed *eccentric connectivity index.*** V. Kumar, S. Satish, and M.A. Kumar* [MD U] **See Applications, QSAR.**

408-417 **Closing loop base pairs in RNA loop–loop complexes: Structural behavior, interaction energy and solvation analysis through molecular dynamics simulations**, J. Golebiowski* [U Nice-Sophia Antipolis], S. Antonczak, J. Fernandez-Carmona, R. Condom and D.C. Bass

The water-mediated GA closing base pair showed an interaction energy similar to that found on fully geometry-optimized structure, the water-mediated CU closing base pair interaction energy reaches less than half the optimal value.

418-426 **A DFT investigation of conformational geometries and interconversion equilibria of phenylthiosemicarbazone and its complexation with zinc.** V. Ruangpornvisuti* [Chulalongkorn U] and B. Wanno.

Conformational pathways for tautomerizations and interconversions of HAPhTSC conformers were presented. The geometry of the zinc complex with HAPhTSC is founded as a $Zn(HAPhTSC)_2Cl_2$ structure and binding of this complex is an exothermic and spontaneous reaction.

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1-1 **Introducing the *Journal of Chemical Theory and Computation*.** W.L. Jorgensen

JCTC is a new journal from the American Chemical Society.

2-13 **An efficient linear-scaling ewald method for long-range electrostatic interactions in combined QM/MM calculations.** K. Nam, J. Gao, and D.M. York* [U Minnesota]

See **Methodology-QM/MM**.

14-23 **Neural Network Models of Potential Energy Surfaces: Prototypical Examples.** J.B. Witkoskie and D.J. Doren* [U Delaware]

A neural network method of generating potential energy surfaces quickly is described, parameterized, and applied to simple examples.

24-35 **Parameterization of Reversible Digitally Filtered Molecular Dynamics simulations.** A.P. Wiley, M.T. Swain, S.C. Phillips, J.W. Essex* [U Southampton], and C.M. Edge

See **Methodology-Potentials and Parameters**

41-53 **New Effective Core Method (Effective Core Potential and Valence Basis Set) for Al Clusters and Nanoparticles and Heteronuclear Al-Containing Molecules.** N.E. Schultz and D.G. Truhlar* [U Minnesota]

A newly developed Minnesota effective core (MEC) method for aluminum is comprised of an effective core potential method for Al and a polarized valence triple-ζ basis set for Al.

54-60 **Use of block Hessians for the optimization of molecular geometries.** J. Pu and D.G. Truhlar* [U Minnesota]

See **Methodology-Conformational Search and Analysis**

61-69 **Using Hessian updating to increase the efficiency of a Hessian based predictor-corrector reaction path following method.** H.P. Hratchian and H.B. Schlegel* [Wayne State U]

Hessian updating schemes are used to speed up calculation of intrinsic reaction coordinates in chemical reactions simulations.

70-77 **Benchmarking the conductor-like polarizable continuum model (CPCM) for aqueous solvation free energies of neutral and ionic organic molecules.** Y. Takano and K.N. Houk* [UCLA]

See **Methodology-Solvation Energy**

78-82 **Adsorption of water molecules on flat and stepped nickel surfaces from first principles.** D. Sebastiani and L.D. Site* [Max-Planck Institut Polymer Research]

DFT calculations are used to understand the adsorption of water oligomers to nickel surfaces.

83-86 **An aromaticity scale based on the topological analysis of the electron localization function including _ and _ contributions.** J.C. Santos* [U Tecnica Federico Santa Maria], J. Andres, A. Aizman, and P. Fuentealba

A quantitative aromaticity scale using the average bifurcation value of the electron localization function is described, validated, and applied to aluminum based clusters.

87-94 **A simple mathematical model for the cooperative and competitive substituent effects found in the cope rearrangements of phenyl-substituted 1,5-hexadienes.** D.A. Hrovat and W.T. Borden [U Washington]

A mathematical model describes the dependence of the Cope transition state energy on the presence and placement of radical stabilizing substituents.

95-106 **Computational and spectroscopic studies of Re(I) bipyridyl complexes containing 2,6-dimethylphenylisocyanide (CNx) ligand.** S.R. Stoyanov, J.M. Villegas, A.J. Cruz, L.L. Lockyear, J.H. Reibenspies, and D.P. Rillema* [Wichita State U]

Computational, electronic absorption, and excited-state emission studies of a series of Re(I) bipyridine complexes are described.

107-116 **Modeling the morphology and phase stability of TiO2 nanocrystals in water.** A.S. Barnard* [Argonne], P. Zapol, and L.A. Curtiss

A previously described thermodynamic model of nanoparticles as a function of size and shape is used to examine the relative phase stability of nanoscale anatase and rutile in water.

117-129 **Normal-mode analysis of circular DNA at the base-pair level. 1. Comparison of computed motions with the predicted behavior of an ideal elastic rod.** A. Matsumoto, I. Tobias, and W.K. Olson* [Rutgers]

Low frequency normal modes that underlie the bending, twisting, and stretching of closed circular DNA are analyzed and the results are compared with those from an ideal elastic rod model.

130-142 **Normal-mode analysis of circular DNA at the base-pair level. 2. Large-scale configurational transformation of a naturally curved molecule.** A. Matsumoto, I. Tobias, and W.K. Olson* [Rutgers]

A naturally curved 200 bp closed circular DNA molecule is analyzed using normal-mode analysis.

143-152 **Rapid estimation of solvation energy for simulations of protein-protein association.** D.S. Cerutti* [UC San Diego], L.F. Ten Eyck, and J.A. McCammon

See **Methodology-Solvation Energy**

153-168 **Determination of electrostatic parameters for a polarizable force field based on the classical drude oscillator.** V.M. Anisimov, G. Lamoureux, I.V. Vorobyov, N. Huang, B. Roux, and A.D. MacKerell, Jr.* [U Maryland]

See **Methodology-Potentials and Parameters**

169-180 **Efficient simulation method for polarizable protein force fields: Application to the simulation of BPTI in liquid water.** E. Harder, B. Kim, R.A. Friesner, and B.J. Berne* [Columbia U]

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