Results

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About 79 papers from 12 journals are cited.

Editorial and News

This will be the final issue, after 14 volumes, of this newsletter. I know it has been very valuable to many, and that the field has been benefited by this routine digest, but have been unable to find a suitable replacement editor. If it becomes possible to continue, we will contact you. In the mean time, the editors wish you the very best in your modeling efforts, and, while we are at it, a Merry Christmas and Happy New Year.

David D. Busath, Editor

1. APPLICATIONS

1.1. *Small Molecules*

Water and Solvation

SM6: A density functional theory continuum solvation model for calculating aqueous solvation free energies of neutrals, ions, and solute-water clusters.

C.P. Kelly, C. J. Cramer, and D.G. Truhlar* [U Minnesota]

J. Chem. Theory and Comput. **1**, 1133-1152 (2005)

Using a database of aqueous solvation free energies for 273 neutrals, 112 ions, and 31 ion-water clusters, parameter sets for the mPW0 hybrid density functional were optimized and new charge and continuum solvent models, Charge Model 4 (CM4), Solvation Model 6 (SM6), are described. SM6 is the only model that improves when an explicit solvent molecule is added to solutes with concentrated charge densities. SM6 retains its accuracy when used in conjunction with the B3LYP and B3PW91 functionals.

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 (2005)

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

Mechanism of molecular diffusion in ice crystals.

T. Ikeda-Fukazawa* [Japan Sci & Tech Agency],
K. Kawamura, and T. Hondoh

Mol. Sim. **30**, 973-979 (2005)

MD simulations are used to investigate the diffusion of O_2, N_2, CH_4, and CO_2 in a crystal of ice Ih. The diffusion mechanism for the molecules differs significantly from the interstitial mechanism that applies to atoms such as helium. The air molecules hopped between stable sites by a new mechanism called the breaking-bond mechanism in which hydrogen bonds in the lattice are broken. The repulsive interactive between the air and water molecules in ice is the dominant factor governing the diffusion mechanism.

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Marginal symbols indicate that the authors acknowledged the use of a software package from a commercial sourse. **A** refers to Accelrys Inc. and **T** to Tripos Inc. Other companies are denoted by their name in a box. Papers of special interest are marked by an exclamation point.

Organic Solvents

Thermal stability of benzorods: Molecular-dynamics simulations.

O.B. Malcioglu and S. Erkoc* [Middle East TechU]

J. Mol. Graph. Mod. **24**, 213-218 (2005)

MD simulations investigated the thermal stability of benzorods, obtained by stacking *n* (*n*=2-20) dehydrogenated benzene. The results showed that these structures assume a geometrical form that depends on the number of dehydrogenated benzene layers, and are stable under heat treatment up to elevated temperatures with a dependence on length.

Asymptotic trends in thermodynamic perturbation theory.

J.R. Elliott and N.H. Gray* [U Akron]

J. Chem. Phys. **123,** 18490201-18490206 (2005)

A study of the components in thermodynamic perturbation theory for evaporation of alkanes ranging from 3-80 carbons indicates that segments of up to 10 carbons per course-grained segment are appropriate.

Medicinal Chemistry and Drug Design

Modeling of activity of cyclic urea HIV-1 protease inhibitors using regularized-artificial neural networks.

M. Fernández and J. Caballero* [U Matanzas]

Bioorg. Med. Chem. **14,** 280-294 (2006)

Artificial neural networks were used to model both inhibition of HIV-1 protease (K_i) and inhibition of HIV replication for 55 cyclic urea derivatives using constitutional and 2D descriptors. The best non-linear models suggested the influence of the presence of nitrogen atoms and the molecular volume distribution in the inhibitor structures on the HIV-1 protease inhibition. The inhibition of HIV replication was dependent on the occurrence of five-member rings.

Modeling of farnesyltransferase inhibition by some thiol and non-thiol peptidomimetic inhibitors using genetic neural networks and RDF approaches.

M. Pérez González, J. Caballero , A. Tundidor-Camba, A.M. Helguera, and M. Fernández* [U Matanzas]

Bioorg. Med. Chem. **14,** 200-213 (2006)

Inhibition of farnesyltransferase (FT) enzyme by a set of 78 thiol and non-thiol peptidomimetic inhibitors was modeled by a genetic neural network (GNN) approach, using radial distribution function descriptors. Descriptors in the GNN model suggested the occurrence of a strong dependence of FT inhibition on the molecular shape and size rather than on electronegativity or polarizability characteristics of the studied compounds.

Virtual screening of novel CB2 ligands using a comparative model of the human cannabinoid CB2 receptor.

O.M.H. Salo* [U Kuopio], K.H. Raitio, J.R. Savinainen, T. Nevalainen, M. Lahtela-Kakkonen, J.T. Laitinen, T. Järvinen, and A. Poso

J. Med. Chem. **48**, 7166-7171 (2005)

A GOLD docking-based virtual screen of Maybridge compounds against a CB2 GPCR homology model finds a low-potency partial agonist of CB2 (–logEC50=5.3).

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A

Quantitative Structure-Activity Relations

A 4D-QSAR study on anti-HIV HEPT analogues.

A. Bak and J. Polanski* [U Silesia]

Bioorg. Med. Chem. **14**, 273-279 (2006)

4D-QSAR method is coupled with the PLS analysis to investigate the antiviral activity of HEPT, a series of conformationally flexible molecules that bind HIV-1 reverse transcriptase. Hopfinger's and SOM-4D-QSAR models indicated that both methods yield comparable results. The results showed that this method properly indicates the mode of interaction revealed by X-ray studies and allowed us to calculate highly predictive QSAR models.

3D-QSAR analysis on benzazole derivatives as eukaryotic topoisomerase II inhibitors by using comparative molecular field analysis method.

O. Temiz-Arpaci, B. Tekiner-Gulbas, I. Yildiz* [Ankara U], E. Aki-Sener, and I.Yalcin

Bioorg. Med. Chem. **13**, 6354-6359 (2005)

3D-QSAR is used for a series of benzoxazole, benzimidazole, and oxazolo (4,5-b)pyridine derivatives with CoMFA with PLS fit to predict the steric and electrostatic molecular field interactions for the activity. The CoMFA model having r^2 of 0.997 and q^2 value as 0.435. The obtained model reveals that electronegatively charged substituents such as NO_2 or $COOCH_3$ group on position R and/or R_1 at the heterocyclic ring system and positively charged atom and/or atom groups located between the benzazole moiety and 2-substituted phenyl ring as a bridge element improve the activity.

Molecular modeling, design, synthesis, and biological evaluation of novel 3′,4′-dicamphanoyl-(+)-*cis*-khellactone (DCK) analogs as potent anti-HIV agents.

L. Xie*[Beijing Inst Pharm Tox], C. Zhao, T. Zhou, H. Chen, B. Fan, X. Chen, J. Ma, J. Li, Z. Bao, Z. Lo, D. Yu and K.-H. Lee

Bioorg. Med. Chem. **13**, 6435-6449 (2005)

3D-QSAR studies are used to develop new potential anti-AIDS drug candidates of new DCK analogs with improved molecular water solubility. CoMFA and CoMSIA models resulted with r^2 values of 0.995 and 0.987, and q^2 values of 0.662 and 0.657, respectively. Based on these models, 15 new DCK analogs with polar functional groups at the 3-position were subsequently designed, and evaluated against HIV-1 replication in H9 and MT4 cell lines.

QSAR modeling of blood, air and tissue: Air partition coefficients using theoretical descriptors.

A.R. Katritzky* [U Florida], M. Kuanar, D.C. Fara, M. Karelson, W.E. Acree, Jr., V.P. Solov'ev, and A. Varnek

Bioorg. Med. Chem. **13**, 6450-6463 (2005)

CODESSA-PRO and ISIDA programs are employed to predict structural descriptors. CODESSA-PRO is used to develop and validate four and five descriptor regression models on three different test sets. Calculations with ISIDA resulted in models based on atom/bond sequences involving two to three atoms with statistical parameters that were similar to those of models obtained with CODESSA-PRO.

QSAR studies on 1-phenylbenzimidazoles as inhibitors of the platelet-derived growth factor.

A.R. Katritzky* [U Florida], D.A. Dobchev, D.C. Fara, and M. Karelson

Bioorg. Med. Chem. **13,** 6598-6608 (2005)

CODESSA PRO is used with the chemical descriptors that are calculated on geometrical, topological, quantum mechanical, and electronic basis to develop the QSAR models of the biological activity of 123 1-phenylbenzimidazoles as inhibitors of the PDGF receptor. The obtained models, linear regression and nonlinear (artificial neural network), are aimed to link the structures to their reported activity log $1/IC_{50}$.

Quantitative Structure-Activity Relations (cont'd)

QSAR of the testosterone binding globulin affinity by means of correlation weighting of local invariants of the graph of atomic orbitals.

Ivan Raska, Jr.* [Charles U Prague] and A. Toropov

Bioorg. Med. Chem. **13,** 6830-6835 (2005)

The testosterone binding globulin affinity is modeled as a mathematical function of molecular structure in two versions of molecular structure elucidation: firstly by hydrogen-filled molecular graphs (HFG) and secondly by the so-called graphs of atomic orbitals (GAO). Increased orders of Morgan extended connectivity in the HFG and GAO are examined as local invariants. A QSAR was obtained using optimisation of the correlation weights of the above-mentioned invariants.

Synthesis and anti-viral activity of a series of sesquiterpene lactones and analogues in the subgenomic HCV replicon system.

D.-R. Hwang, Y.-S. Wu, C.-W. Chang, T.-W. Lien, W.-C. Chen, U.-K. Tan, J.T.A. Hsu and H.-P. Hsieh* [Nat Health Res Inst]

Bioorg. Med. Chem. **14**, 83-91 (2006)

The structure-activity relationship was elucidated to reveal that the spatial arrangement of the terpenoid skeleton fused with an α-methylene-γ-lactone moiety produces maximal anti-HCV activity. Strong anti-HCV potency indicates a possibility of secondary amino adducts converting back to parthenolide or being replaced by the nucleophilic residues of proteins inside cells.

A new potential cyclooxygenase-2 inhibitor, pyridinic analogue of nimesulide.

C. Michaux* [U Notre Dame de la Paix], C. Charlier, F. Julémont, X. de Leval, J.M. Dogné, B. Pirotte, and F. Durant

Eur. J. Med. Chem. **40**, 1316-1324 (2006)

Docking is performed to investigate the structure-activity relationships for COX-2 inhibitors through the binding mode of original pyridinic compounds structurally related to nimesulide. Structural modifications are proposed to reverse the selectivity of the more active inhibitor of the series characterized by a preferential activity on COX-1. On the basis of these modifications, a new compound with a bromo substituent was designed and showed a COX-2 selective inhibition.

Design, synthesis, and biological evaluation of linear 1-(4-, 3- or 2-methylsulfonylphenyl)-2-phenylacetylenes: A novel class of cyclooxygenase-2 inhibitors.

Q.-H. Chen, P.N. Praveen Rao and E.E. Knaus* [U Alberta]

Bioorg. Med. Chem. **13**, 6425-6433 (2005)

Structure activity studies identified 1-(3-methylsulfonylphenyl)-2-(4-methylphenyl)-acetylene as a potent COX-2 inhibitor with a high COX-2 selectivity index comparable to the reference compound rofecoxib. Molecular modeling study showed that the $MeSO_2$ COX-2 pharmacophore was positioned in the vicinity of the secondary COX-2 binding site near Val^{523}. The structure-activity data acquired indicated that the acetylene moiety constitutes a suitable scaffold (template) to design novel acyclic 1,2-diarylacetylenes with selective COX-2, or dual COX-1/COX-2, inhibitory activities.

Comparative QSAR study of phenol derivatives with the help of density functional theory.

F.A. Pasha* [Bareilly Coll], H.K. Srivastava, and P.P. Singh

Bioorg. Med. Chem. **13,** 6823-6829 (2005)

Four different methods are employed to find the reliability of QSAR study of 50 phenol derivatives. The first model is developed with the help of AM1 calculations and second and third models are designed with the PM3 and PM5 calculations. Finally, DFT calculations are made for the same series of compounds by using a B88-PW91 GGA energy functional with the DZVP basis set. The DFT models have a higher predictive power than AM1, PM3, and PM5 methods.

Zeolites

Modeling proton transfer in zeolites: Convergence behavior of embedded and constrained cluster calculations.

J.T. Fermann, T. Moniz, O. Kiowski, T.J.McIntire, T. Vreven, S.M. Auerbach* [U Massachusetts], and M.J. Frisch

J. Chem. Theory and Computation. **1**, 1232-1239 (2005)

The convergence properties of embedded and constrained cluster models of proton transfer in zeolites are studied by applying DFT to describe clusters and ONIOM to perform the embedding. Convergence to the same values as the constrained clusters was obtained without the use of reactive force fields or periodic boundary conditions in the embedding procedure.

Carbon Nanoparticles

Monolayer-protected nanoparticle-protein interactions.

C. –C. You, M. De, and V.M. Rotello* [U Massachusetts]

Curr. Opi. Chem. Biol. **9,** 639-646 (2005)

Monolayer-protected nanoparticles provided an appealing artificial receptor scaffold for targeting proteins and related biomacromolecules. The present investigations include the molecular recognition of proteins with nanoparticles in aqueous media, self-assembly of proteins and nanoparticles either in solution or on surface, and construction of nanoparticle-based protein sensors.

Applications of carbon nanotubes in drug delivery.

A. Bianco, K. Kostarelos, and M. Prato* [U Trieste]

Curr. Opi. Chem. Biol. 9, 674-679 (2005)

Carbon nanotubes (CNT) are emerging as a new alternative and efficient tool for transporting and translocating therapeutic molecules. CNT is functionalised with bioactive peptides, proteins, nucleic acids and drugs, and used to deliver their cargos to cells and organs. Because functionalised CNT display low toxicity and are not immunogenic, such systems hold great potential in the field of nanobiotechnology and nanomedicine.

Molecular simulation for nanotechnologies: Application to industry.

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

Mol. Sim. **30**, 819-826 (2005)

Molecular simulations are carried out in relation to the nanotechnology and application to industrial problems of electrodeposition in nano-scales and martensite transformation, which are essentially independent to each other. For the free-boundary condition the martensite transformation is rather easy to predict, while for the periodic-boundary condition it has never successfully been obtained so far using MD simulation.

Molecular-dynamics studies on hydrogen atoms in nanostructured graphite.

A. Harada* [Hiroshima U], F. Shimojo, and K. Hoshino

Mol. Sim. **30**, 947- 951 (2005)

Hybrid MD simulation is applied to the model systems to investigate the effect of crystallization on the desorption of hydrogen atoms from nanostructured graphite. The bond between hydrogen and carbon atoms becomes weaker due to the recrystallization of the nanostructured graphite and that the hydrogen dimer is formed with increasing temperature.

Carbon Nanoparticles (cont'd)

A molecular-dynamics simulation study of solvent-induced repulsion between C60 fullerenes in water.

L. Li, D. Bedrov, and Grant D. Smith* [U Utah]

J. Chem. Phys. **123,** 20450401-20450407 (2005)

In contrast to conventional nonpolar solutes, two C60 fullerene molecules repel each other due to water-induced repulsive energy between the two large molecules. The repulsion is due to loss of VDW interactions when the water layer is squeezed out, and the repulsion is overtaken by hydrophobic entropic attraction at high temperature.

1.2. *Biopolymers*

Bioinformatics

External cross-validation for unbiased evaluation of protein family detectors: Application to allergens

D. Soeria-Atmadja, M. Wallman, A.K. Bjorklund, A. Isaksson, U. Hammerling, and M.G. Gustafsson* [Uppsala U]

Proteins **61***,* 918-925 (2005)

The statistical significance of internal LOO validation, external 10-fold cross-validation with a 10% test set and final validation on a large test-set ('holdout') in the design of classifiers for a simulated database and on determination of allergens, are examined critically. The bias introduced by selecting alternative classifiers from the internal LOO, can be removed more efficiently by an 'external cross-validation loop' than by a final 'holdout' validation, and provides useful statistics on different parameter settings.

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An information theoretic approach to macromolecular modeling: I. sequence alignments.

T. Aynechi and I.D. Kuntz* [U Calif San Francisco]

Biophys. J. **89,** 2998-3007 (2005)

Based on information theory, the gap penalty should depend on alphabet size and sequence length

An information theoretic approach to macromolecular modeling: II. force fields

T. Aynechi and I.D. Kuntz* [U Calif San Francisco]

Biophys. J. **89,** 3008-3016 (2005)

From information theory based on lattice models of conformation and simplified alphabets, the information content, and hence force-field resolving power, of long-range specific pairings is greater than close-range and nonspecific pairings.

Protein Structure Prediction

Dependency between consecutive local conformations helps assemble protein structures from secondary structures using Go potential and greedy algorithm

P. Tuffery* [U Paris 7] and P. Derreumaux

Proteins **61***,* 732-740 (2005)

A remarkably simple algorithm is described that uses pre-filtered structure fragments as the basis for local conformational search and sequential (both ways) growth of the protein structure for almost ab-initio structure prediction. The typical RMSD to the target structure is ~5 Å.

Comparative or Homology Modeling

Homology modelling and active-site-mutagenesis study of the catalytic domain of the pneumococcal phosphorylcholine esterase.

N. Eugenia Campillo* [Inst Quim Med], J. Antonio Páez, L. Lagartera, and A. Gonzalez

Bioorg. Med. Chem. **13**, 6404-6413 (2005)

The catalytic domain of pneumococcal phosphorylcholine esterase (Pce), which is capable of removing phosphorycholine residues from teichoic and lipoteichoic acids, was modeled after the x-ray structure of enzymes from the α/β metallo-lactamase family. Docking studies were employed to identify the residues involved in the binding of Zn ions.

Theoretically predicted structures of plasma membrane Ca^{2+}-ATPase and their susceptibilities to oxidation.

G.H. Lushington* [U Kansas], A. Zaidi and M.L. Michaelis

J. Mol. Graph. Mod. **24**, 175-185 (2005)

A 3D-model of PMCA was generated via a combination of homology/comparative modeling, threading, protein-protein docking, and guidance from prior biochemical and analytical studies. The resulting model was validated based on surface polarity/hydrophobicity profiling, standard ProCheck, WhatIF, and PROVE checks, as well as comparison with empirical structure-function observations. This model is used to identify likely oxidation sites.

Ligand docking in the gastric H+/K+-ATPase: Homology modeling of reversible inhibitor binding sites.

C.G. Kim, J.A. Watts, and A. Watts* [Oxford U]

J. Med. Chem. **48**, 7145-7152 (2005)

A homology model of H+/K+-ATPase using a Ca2+-ATPase crystal structure, combined with docking, NMR conformation data, and site-directed mutagenesis suggests a binding site for TMPFPIP that is in the loops between TM5, TM6, and TM8.

Protein Folding

Sterics and solvation winnow accessible conformational space for unfolded proteins.

N.C. Fitzkee and G.D. Rose* [Johns Hopkins U]

J. Mol. Biol. **353**, 873-887 (2005)

Steric hindrance and hydrogen-bonding restrict the conformational space of unfolded proteins. Simulation of short peptides using a five-state approximation of protein allows quantification of conformational restriction, and the authors extrapolate the results to arbitrary length proteins.

Symmetric connectivity of secondary structure elements enhances the diversity of folding pathways.

D.K. Klimov* [George Mason U] and D. Thirumalai

J. Mol. Biol. **353**, 1171-1186 (2005)

Analysis using Go-type models finds that even distribution of alpha helix and beta strand elements tends to result in more diverse folding pathways, while if the distribution of either secondary structure element is localized to different parts of the sequence there is a restricted set of folding pathways.

Reproducible polypeptide folding and structure prediction using molecular dynamics simulations.

M.M. Seibert, A. Patriksson, B. Hess and D. van der Spoel* [Uppsala U]

J. Mol. Biol. **354**, 173-183 (2005

Replica exchange molecular dynamics of chignolin, a β-hairpin peptide, yields an order of magnitude faster sampling of native structure compared to classical MD. Comparison of simulations performed in vacuum and water highlight the role of water in protein folding.

Protein Folding (cont'd)

Folding behavior of chaperonin-mediated substrate protein

W.X. Xu, J. Wang, and W. Wang* [Nanjing U]

Proteins **61**, 777-794 (2005)

The folding behaviour of a model lattice protein in a Go-type potential inside a cavity is studied. Folding rate increases with decreasing cavity wall affinity and has a maximum in the cavity radius. Free energy landscapes, folding events and effects of mutations in a model of chymotrypsin inhibitor 2 are discussed.

Free energy landscape and folding mechanism of a beta-hairpin in explicit water: A replica exchange molecular dynamics study

P.H. Nguyen* [JW Goethe U], G. Stock, E. Mittag, C.K. Hu, and M.S. Li* [Polish Ac Sci]

Proteins **61**, 795-808 (2005)

REMD simulations in Gromacs using the Gromos 43a1 forcefield support the hydrophoic collapse/core formation seen in simulations with other atomic forcefields, but not in off-lattice simple models. Dominant states are the native and molten globule, with a broad transition region, and were identified from a free energy landscape with R_g of the hydrophobic core *vs.* the number of native H-bonds.

Protein Design and Engineering

Electrostatics in computational protein design.

C.L. Vizcarra and S.L. Mayo* [Calif Inst Tech]

Curr. Opi. Chem. Biol. **9**, 622-626 (2005).

Recent progress in modeling electrostatic interactions in computational protein design, with particular emphasis on continuum models, is reviewed.

Protein Electrostatics and Titration

Electrostatics of the intracellular vestibule of K+ channels.

V. Jogini and B. Roux* [Cornell U]

J. Mol. Biol. **354**, 272-288 (2005)

Continuum electrostatics calculations on KcsA finds that as the channel opens, an ion residing in a vestibular cavity common to all potassium channels becomes significantly destabilized.

Electrostatic potential at the retinal of three archaeal rhodopsins: Implications for their different absorption spectra

E. Kloppmann, T. Becker, and G.M. Ullmann* [Bayreuth]

Proteins **61**, 953-965 (2005)

Using the electrostatic potential at the retinal surface due to protein, bilayer and solvent salt from MEAD/LPBE calculations and decomposing it for contributions of single residues, the differences in absorption spectra of bacteriorhodopsin, halorhodopsin and sensory rhodopsin II could be attributed mainly three residues in the retinal binding pocket (Ser141, Thr142 and Ala215 in BR) one close to the pocket (Thr121 in BR) and three at more than 8 Å (Asn76, Glu194 and Glu204 in BR).

Very fast empirical prediction and rationalization of protein pK(a) values

H. Li, A.D. Robertson, and J.H. Jensen* [U Iowa]

Proteins **61**, 704-721 (2005)

Using several simple empirical forumulae, measured pKa's are predicted surprisingly well, comparable to other methods but using only seconds of CPU time, and finally applied to 285 residues in 44 proteins yielding an RMS error of 0.79 units. Properties of different residue types and main structural determinants are discussed.

Protein Dynamics

Comparative molecular dynamics - Similar folds and similar motions?

A. Pang, Y. Arinaminpathy, M.S. Sansom, and P.C. Biggin* [U Oxford]

Proteins **61**, 809-822 (2005)

Extensive MD simulations (290ns in total) of members of the periplasmic binding-protein-like family using Gromacs show large-scale motions to be largely conserved, and smaller motions reflect differences between sequences. Ligand-binding attenuates motions, but otherwise does not interfere. The observation of both opening and closing transitions, leads to the conclusion that low RMSD is not always a measure of simulation quality.

Unwinding the helical linker of calcium-loaded calmodulin: A molecular dynamics study

G. Fiorin, R.R. Biekofsky, A. Pastore, and P. Carloni* [SISSA]

Proteins **61**, 829-839 (2005)

MD simulations of Ca^{2+}-bound Calmodulin show unwinding of the central helix, starting in the middle. From the effects observed, both the solution and X-ray structures can be explained, as well as other (solution-state) experimental data. Details of the transition and effects of different ionic strength, forcefields and simulation parameters are discussed.

A salt-bridge motif involved in ligand binding and large-scale domain motions of the maltose-binding protein.

T. Stockner, H.J. Vogel, and D.P. Tieleman* [U Calgary]

Biophys. J. **89,** 3362-3371 (2005)

"A salt bridge between Glu-111 and Lys-15 forms that effectively locks the protein-ligand complex in a semiclosed conformation inhibiting any further opening and promoting complete closure", which probably plays a "role in the initial steps of substrate transport."

Ligand Binding

Evaluating the molecular mechanics Poisson-Boltzmann surface area free energy method using a congeneric series of ligands to p38 MAP kinase.

D.A. Pearlman* [Science]

J. Med. Chem. **48**, 7796-7807 (2005)

A study applying MM/PBSA for prediction of 16 p38 inhibitors finds that it performs poorly relative to other available methods that take less amounts of CPU time, including thermodynamic integration and OWFEG. The study also finds MM/PBSA yields improved prediction with use of a longer MD simulation and separate MD runs for the complex, protein, and ligand.

Docking studies and ligand recognition in folylpolyglutamate synthetase.

X.-J. Tan and H.A. Carlson* [U Michigan]

J. Med. Chem. **48**, 7764-7772 (2005)

Docking suggests that folylpolyglutamate synthetase accommodates ligands of different length and net charge through two separate binding sites instead of just the one binding site currently known.

Enzyme Catalysis

An implementation of the nudged elastic band algorithm and application to the reaction mechanism of HGXPRTase from *Plasmodium falciparum.*

R. Crehuet*[CSIC], A. Thomas, and M.J. Field

J. Mol. Graph. Mod. **24**, 102-110 (2005)

The nudged elastic band algorithm was used in the simulation program DYNAMO with some modifications to the original algorithm to improve its efficiency. The method is applied to the reaction mechanism of the enzyme hypoxanthine-guanine-xanthine phosphoribosyltransferase from *Plasmodium falciparum*.

Enzyme Catalysis (cont'd)

Effects of calcium binding on structure and autolysis regulation in trypsins: A molecular dynamics investigation.

E. Papaleo, P. Fantucci, and L. De Gioia*
[Univ. of Milano-Bicocca]

J.Chem.Theory and Computation. **1,** 1286-1297 (2005)

In MD simulations, calcium-free trypsins are characterized by a more flexible structure, connecting Ca^{2+} binding and autoproteolysis propensity. The removal of Ca^{2+} not only increases the flexibility of regions around its binding site (in the N-terminal domain), but leads to channeling of the fluctuations to remote sites in the C-terminal domain, possibly involving the interdomain loop.

Insights into the induced fit mechanism in antithrombin-heparin interaction using molecular dynamics simulations.

H. Verli and J.A. Guimarães* [U Fed do Rio Grande do Sul]

J. Mol. Graph. Mod. **24**, 203-212 (2005)

MD simulations are used to study the interaction between a pentasaccharide and AT. The results suggested that there is no conformational requirement for the ligand to bind, and the impact of binding on AT structure is explored.

Accurate QM/MM free energy calculations of enzyme reactions: Methylation by catechol *O*-methyltransferase.

T.H. Rod* [Lund U] and U. Ryde

J. Chem. Theory and Computation. **1**, 1240-1251 (2005)

Quantum mechanical thermodynamic cycle perturbation (QTCP) and QM/MM-FE methods are applied to the methylation of catecholate catalyzed by catechol O-methyltransferase. The free energy barrier for the reaction was estimated by computing free energy changes in steps between fixed QM regions along a predetermined reaction pathway. In this method, the QM region is fixed. The approximation leads to well-converged free energy barriers.

A quantum chemical study on the mechanism of glycinamide ribonucleotide transformylase inhibitor: 10-Formyl-5,8,10-trideazafolic acid.

Q.-A. Qiao* [Yantai Normal U], Y. Jin, C. Yang, Z. Zhang, and M. Wang

J. Biophys. Chem.**118**, 78-83 (2005)

DFT is used to study the reaction mechanism of glycinamide ribonucleotide (GAR) with 10-formyl-5,8,10-trideazafolic acid (10f-TDAF). The results indicated that inhibitor 10f-TDAF could form a very stable intermediate with the substrate GAR or generated an imine bond with GAR by elimination of water. The results examined the presumption from available experiments and implied that 10f-TDAF is an important target for anti-neoplastic intervention.

Assessment of a mechanism for reactive inhibition of carboxypeptidase-A with QM/MM methods.

L. Phoon and N.A. Burton* [U Manchester]

J. Mol. Graph. Mod. **24**, 94-101 (2005)

QM/MM methods were used to investigate the mechanism of inhibition of carboxypeptidase-A (CPA) by the two enantiomers of a reactive inhibitor, *N*-(2-chloroethyl)-*N*-methylphenylalanine. The results showed that the enzyme active site is flexible enough to allow the nucleophilic deactivation reactions of both the (*R*) and (*S*) forms of a model of the inhibitor to be catalysed by the Zn(II) cofactor of CPA.

Protein-Protein Interactions

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Survey of the geometric association of domain-domain interfaces

W.K. Kim and J.C. Ison* [EBI]

Proteins **61**, 1075-1088 (2005)

A rapid method for analyzing the conservation of domain interfaces from 'facial' and 'inter-facial' geometric arrangements using 1D 'interface tags' is described, applied to a non-redundant set of ~4000 interfaces from ~49,000 pairs of which ~11,000 intramolecular, and critically evaluated. On average there is more than one interface per family, and distinct and mostly well-separated faces are used for different partners. The arrangement of interface residues is highly conserved over large evolutionary distance.

Membrane Proteins and Lipid-Peptide Interactions

Membrane protein structure quality in molecular dynamics simulation.

R.J. Law* [U Oxford], C. Capener, M. Baaden, P.J. Bond, J. Campbell, G. Patargias, Y. Arinaminpathy, and M.S.P. Sansom

J. Mol. Graph. Mod. **24**, 157-165 (2005)

The relationship between model stability in MD simulations derived from RMSD and structure quality assessment from various protein quality checkers was examined. The results were compared to membrane protein structures, solved at various resolution, by either X-ray or electron diffraction techniques. The checking programs predicted the potential success of MD in making functional conclusions. MD stability was a good indicator for the quality of structures and was dependent on the resolution at which the structures were determined.

Proteins and Surfaces

An intuitive approach to measuring protein surface curvature

R.G. Coleman, M.A. Burr, D.L. Souvaine, and A.C. Cheng* [Pfizer]

Proteins **61**, 1068-1074 (2005)

A robust, non-iterative method is described to define surface curvature as defined by fitting spheres to the surface, which is usually done iteratively in a complex method that is less robust. 'Patch-size' can be adusted to resolve features at different length scales. Differences in quality, interpretability and calculation speed are discussed.

Nucleic Acids

A semiempirical quantum model for hydrogen-bonded nucleic acid base pairs.

T.J. Giese, E.C. Sherer, C.J. Cramer, and D.M. York* [U Minnesota]

J. Chem. Theory and Computation. **1**, 1275-1285 (2005)

A semiempirical Hamiltonian ($PM3_{BP}$) was developed to model hydrogen bonding in nucleic acid base pairs. The $PM3_{BP}$ Hamiltonian is a novel reparametrization of the PM3 Hamiltonian designed to reproduce experimental base pair dimer enthalpies and high-level density-functional results. The results are compared with experimental values and with benchmark density-functional (*m*PWPW91/MIDI!) calculations for hydrogen-bonded nucleic acid dimers and trimers.

Nucleic Acids (cont'd)

A combined QM and MM investigation into guanine quadruplexes.

E.H. Clay and I.R. Gould* [Imperial College]

J. Mol. Graph. Mod. **24**, 138-146 (2005)

QM energy calculations, optimisations and MD simulations are used to investigate the stability of a human telomeric guanine quadruplex containing potassium and sodium cations. G-quadruplexes may offer a novel path to cancer inhibition. QM investigation of the G_{12}-quadruplex core containing no cations unsurprisingly yields a highly unfavourable energetic structure. MD simulation of the sodium containing quadruplex for 4 ns showed significant structural reorganisation compared with the original potassium containing crystal structure.

Lipids and Surfactants

Interactions of liquid crystal-forming molecules with phospholipid bilayers studied by molecular dynamics simulations.

E.B. Kim, N. Lockwood, M. Chopra, O. Guzmán, N.L. Abbott and J.J. de Pablo* [U Wisconsin]

Biophys. J. **89,** 3141-3158 (2005)

Experiments using liquid crystals to image cell membranes were simulated by MD. The potential of mean force of 4-cyano-4'-pentylbiphenyl (5CB) and 4'-(3,4-difluor-phenyl)-4-pentyl-bicylohexyl (5CF) shows a dramatic well in the bilayer, apparently related to enhanced acyl chain order and head group structural changes.

Molecular dynamics study of bipolar tetraether lipid membranes.

W. Shinoda* [AIST], K. Shinoda, T. Baba, and M. Mikami

Biophys. J. **89**, 3195-3202 (2005)

MD simulations of bilayers composed of tetraether and diether archael lipids, with or without covalent connections at the ends of the tails to form macrocyles, show the tetraether bilayers to have lower area per headgroup and lateral mobility (10x). The macrocyle has higher elastic expansion modulus (3x) than its counterpart.

A molecular-dynamics study of lipid bilayers: Effects of the hydrocarbon chain length on permeability.

T. Sugii, S. Takagi, and Y. Matsumoto* [U Tokyo]

J. Chem. Phys. **123**, 18471401-18471408 (2005)

The Widom cavity insertion and probability ratio methods indicate that the free energy barriers for O_2, CO, and NO is broader and higher for DPPC than for DLPC, whereas water permeability, based on the solubility-diffusion model and diffusion coefficients obtained from the force or velocity autocorrelation methods, is little affected by lipid chain length.

1.3. Polymers

Sorption mechanism of aromatic molecules in the interface between liquid and polymer crystal.

Y. Tamai* [U Fului] and M. Fukuda

Mol. Sim. **30**, 901-906 (2005)

MD simulations are used to investigate the sorption-desorption mechanism of the aromatic molecules in the δ form for the interface between liquid benzene and the δ form of crystalline syndiotactic polystyrene. In the single crystal of the δ form, no translational diffusion of benzene was observed, and in the liquid interface, the sorption of the benzene molecules was observed. It was observed that the ordering of the liquid on the surface of the polymer crystal plays an important role in the sorption mechanism.

Polymers (cont'd)

Molecular dynamics simulation of discontinuous volume phase transitions in highly-charged crosslinked polyelectrolyte networks with explicit counterions in good solvent.

D.-W. Yin, Q. Yan, and J.J. de Pablo*
[U Wisconsin-Madison]

J. Chem. Phys. **123,** 17490901-17490909 (2005)

This paper details numerous electrostatic and excluded-volume characteristics of an organized polyelectrolyte network with explicit counterions and implicit solvation.

1.4. Surfaces, Catalysts, and Material Subjects

Theoretical study of aluminum arsenide clusters: Equilibrium geometries and electronic structures of Al_nAs_n (n = 1-4).

Y. Qu* [Shandong Inst Light Industry], W. Ma, X. Bian, H. Tang, and W. Tian

J. Mol. Graph. Mod. **24**, 167-174 (2005)

DFT was used to investigate the geometry, electronic configurations, harmonic vibrational frequencies and stability of the structural isomers of Al_nAs_n clusters (n = 1-4). The Al-As bond dominates the structures for many isomers so that one preferred dissociation channel is loss of the AlAs monomer. Comparisons with valence-isoelectronic Si2n, AlnPn and GanAsn clusters of same size, the properties of the aluminum arsenide clusters are analogous to those of their corresponding AlnPn, Si2n counterparts. The results explained the modification and refinement of the Si phase in Al-Si alloy at the molecular level.

Local behavior of water molecules on brucite, talc, and halite surfaces: A molecular dynamics study.

H. Sakuma* [Tohoku Univ.], T. Tsuchiya, K. Kawamura, and K. Otsuki

Mol. Sim. **30**, 861-871 (2005)

MD simulations are used to calculate the structural and dynamic properties of water between brucite (0001), talc (001), and halite (100) surfaces at ambient conditions. The interaction potential models between water and the minerals are developed by the energy curves obtained from *ab initio* electronic state calculations. The self-diffusion coefficients parallel to the surfaces are enhanced in the vicinity of brucite and talc surfaces, and reduced on halite surface compared with that in bulk.

2. METHODOLOGY

Quantitative Structure-Activity Relations

Conformationally sampled pharmacophore for peptidic δ-opioid ligands.

D. Bernard, A. Coop, and A.D. MacKerell Jr* [U Maryland]

J. Med. Chem. **48**, 7773-7780 (2005)

A new pharmacophore elucidation method is developed in the context of δ-opioid ligands. The method involves extensive MD conformational sampling of the ligand, followed by elucidation of a pharmacophore that differentiates agonists and antagonists.

Potentials and Parameters

Development of parameter sets for semi-empirical MO calculations of transition metal systems: Iron parameters for iron-sulfur proteins.

J.P. McNamara, M. Sundararajan, and I.H. Hillier* [U Manchester]

J. Mol. Graph. Mod. **24**, 128-137 (2005)

A semi-empirical parameter set for iron was developed for the study of iron-sulfur proteins having a single iron atom using the BFGS optimization procedure They were then tested on a set of model complexes with various ligands and showed good agreement with both DFT and experimental data.

A physically meaningful method for the comparison of potential energy functions.

J.L. Alonso and P. Echenique* [BIFI, U Zaragoza]

J. Comput. Chem. **27,** 238-252 (2006)

A quantitative technique for comparing force fields with statistical meaning and that avoids overestimating the distance between potentials is presented. Usage is illustrated with the VDW energy of the Trp-Cage protein and comparison of different levels of theory for alanine dipeptide torsions.

Interatomic potential models for natural apatite crystals: Incorporating strontium and the lanthanides.

J.A.L. Rabone* [Birkbeck College London] and N.H. De Leeuw

J. Comput. Chem. **27,** 253-266 (2006)

Parameters derived from crystal structures using GULP are illustrated by "predicted enthalpies of mixing of strontium and calcium apatites and predicted cation site preferences in strontium calcium fluorapatite."

Monte-Carlo Simulation

Multibaric-multithermal ensemble simulation for simple liquids.

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

Mol. Sim. **30**, 847-852 (2005)

A generalized isobaric-isothermal ensemble MC algorithm is presented, referred as the multibaric-multithermal algorithm. The algorithm allows a random walk that widely explores volume space and potential energy space, as illustrated with a Lennard-Jones 12-6 potential system.

Monte Carlo simulations of biomolecules: The MC module in CHARMM.

J. Hu, A. Ma, and A.R. Dinner* [U Chicago]

J. Comput. Chem. **27,** 203-216 (2006)

A new module in CHARMM allows MC with several predefined types of moves. "Sampling can be enhanced by noncanonical acceptance criteria, automatic optimization of step sizes, and energy minimization." It is easy to use and very efficient.

Efficient Monte Carlo trial moves for polypeptide simulations.

M.R. Betancourt* [IUPUI]

J. Chem. Phys. **123,** 17490501-17490507 (2005)

An MC move consisting of a rigid rotation of a peptide segment between two arbitrarily separated alpha carbons is easy to compute and efficient for searching protein conformational space. Only φ and ψ dihedral angles and Cα bond angles at the end of the segment are affected, and the latter can be confined to within 10º of the native angle without loss of usefulness.

QM/MM

An efficient real space multigrid QM/MM electrostatic coupling.

T. Laino* [Scuola Normale Superiore di Pisa], F. Mohamed, A. Laio, and M. Parrinello

J. Chem. Theory and Computation. **1**, 1176-1184 (2005)

A novel real space multigrid approach that handles coulomb interactions very effectively and that is implemented in the CP2K code is presented. This novel scheme does not need fine-tuning or adjustable parameters, and it is quite accurate, leading to a dynamics with very good energy conservation. It is validated with simulations of water and of a zwitterionic dipeptide solvated in water.

Ligand Docking

Scoring binding affinity of multiple ligands using implicit solvent and a single molecular dynamics trajectory: Application to *Influenza* neuraminidase.

P. Bonnet and R.A. Bryce* [U Manchester]

J. Mol. Graph. Mod. **24**, 147-156 (2005)

A perturbative approach is developed to calculate the binding free energy of multiple ligands, based on a single molecular dynamics simulation of a reference ligand-receptor complex and analysis via a hybrid force field/continuum model potential. This methodology is applied to prediction of relative binding free energies of 10 *Influenza* neuraminidase inhibitors, using Poisson-Boltzmann and generalized Born models of implicit solvent. These single-step MM-PB/SA and MM-GB/SA approaches predicted the experimentally most potent ligand as first- or second-ranked according to total binding free energy.

Statistical tools for virtual screening.

J.R. Krumrine, A.T. Maynard, and C.L. Lerman* [Astra-Zeneca]

J. Med. Chem. **48**, 7477-7481 (2005)

Docking campaigns often result in a large number of hits that cannot all be tested. The authors present statistical methods for prioritization of docking hits including (1) using statistical significance of hit series, and (2) docking and testing only selected (e.g., 30) compound cluster representatives.

Combining in silico tools and NMR data to validate protein-ligand structural models: Application to matrix metalloproteinases.

I. Bertini* [U Florence], M. Fragai, A. Giachetti, C. Luchinat, M. Maletta, G. Parigi, and K.J. Yeo

J. Med. Chem. **48**, 7544-7559 (2005)

Relatively rapid determination of protein-ligand models can be had starting from a known protein model and using using HSQC to determine the ligand binding site. Docking models are then used to predict NOEs, and the model is either rejected or refined based on ^{15}N HSQC NOESY experimental data.

!

Molecular docking of balanol to dynamics snapshots of protein kinase A

C.F. Wong* [U Missouri-St. Louis], J. Kua, Y. Zhang, T.P. Straatsma, and J.A. McCammon

Proteins **61**, 850-858 (2005)

An attempt is made to explicitly include ligand-induced changes in receptor conformations. Docking balanol into snapshots from MD simulations of balanol-bound PKA was more succesfull into snapshots from MD without balanol bound. The X-ray conformation could be identified reliably from the largest low-energy cluster, but not from AutoDock scoring nor Amber7/GBSA energies.

Molecular Graphics

Rendering of quantum topological atoms and bonds.

M. Rafat, M. Devereux, and P.L.A. Popelier*[U Manchester]

J. Mol. Graph. Mod. **24**, 111-120 (2005)

An algorithm for the visualization of atoms and bonds in molecules and van der Waals complexes, based on the topology of the electron density, is described. In conjunction with the graphical user interface of the computer program MORPHY, it enables robust and efficient rendering of complicated interatomic surfaces, as are found in larger systems.

Computational tools for the analysis and visualization of multiple protein-ligand complexes.

S.E. O'Brien* [Pfizer Global R&D], D.G. Brown, J.E. Mills, C. Phillips, and G. Morris

J. Mol. Graph. Mod. **24**, 186-194 (2005)

Computational tools are described that analyse and display multiple protein-ligand interactions and their properties in a simplified way. A novel binding-mode similarity metric, able to cluster 20 ligands complexed to HIV-1 reverse transcriptase into distinct groups, is illustrated. 2-D and 3-D similarities are combined to provide enhanced understanding, as illustrated with 33 factor Xa inhibitor complexes.

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