Results

MOLECULAR MODELING & COMPUTATIONAL CHEMISTRY

Vol. 14, No. 6 **1 July 2005**

Coverage period: 1 June 2005 through 30 June 2005
About 67 papers from 15 journals are cited.

Editorial and News

Several articles focused on mesoscopic modeling of lipid bilayers with an emphasis on their mechanical properties.

As mentioned last month, the majority of the journal reviews are now simply covered in the main section of the newsletter.

Otherwise, things have been rather quiet this month. I would just call your attention to a few highlighted articles, particularly in the Methodology section.

David D. Busath, Editor

1. APPLICATIONS

1.1. *Small Molecules*

General and Model Systems

A potential model for the study of ices and amorphous water: TIP4P/Ice.

J. L. F. Abascal* [U Complutense], E. Sanz, R. García Fernández, and C. Vega.

J. Chem. Phys. **122**, 23451101-23451109 (2005)

None of the rigid water models predict ice phase coexistence curves accurately, though TIP4P is the closest. After TIP4P is tuned to give accurate melting of hexagonal phase ice at 1 bar (272.2 K), it gave better coexistence curves for the other types of ice and for ice density.

Water and Solvation

Water models based on a single potential energy surface and different molecular degrees of freedom.

H. Saint-Martin* [U Nac Autónoma de México], J. Hernández-Cobos, and I. Ortega-Blake

J. Chem. Phys. **122**, 22450901- 22450912 (2005)

Neglect of polarizability and flexibility in water molecules has little effect if average values are used that are appropriate for the phase under consideration. An approach is developed to adapt the averages for conditions, which should allow a unified simplified model.

Organic Solvents

Investigation of benzene-hexafluorobenzene dynamics in liquid binary mixtures.

M.D. Elola* [Colorado State U] and B.M. Ladanyi

J. Chem. Phys. **122**, 22450801-22450815 (2005)

After softening the Lorentz–Berthelot combining rules by 50% for H-F interactions (to avoid overestimating the energy of mixing), the autocorrelation functions indicate face-to-face dimers of benzene and hexafluorobenzene.

Hydrogen bonding in ethanol under shear.

J. Petravic* [Australian Natl U] and J. Delhommelle

J. Chem. Phys. **122**, 23450901-23450905 (2005)

Sheer thinning occurs when there is hydrogen bond allignment with the direction of sheer forces, although hydrogen bond breakage is induced at low sheer rates.

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

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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.

Medicinal Chemistry and Drug Design

Structure-based design of novel Chk1 inhibitors: Insights into hydrogen bonding and protein-ligand affinity.

N. Foloppe* [Vernalis], L.M. Fisher, R. Howes, P. Kierstan, A. Potter, A.G.S. Robertson, and A.E. Surgenor

J. Med. Chem. **48**, 4332-4345 (2005)

Modeled compound docking binding modes are compared to the subsequently obtained co-crystal structures. Analysis of two of the Chk1 inhibitors finds that the hydrogen bond contributes less than 1.4 kcal/mol to binding.

Modeling of purine derivatives transport across cell membranes based on their partition coefficient determination and quantum chemical calculations.

M. Hoffmann* [A Mickiewicz U], M. Chrzanowska* [A Mickiewicz U], T. Hermann, and J. Rychlewski

J. Med. Chem. **48**, 4482-4486 (2005)

Quantum chemical calculations using a solvent model predicts that MAZA and AZA have similar electrostatic potential surfaces, but MAZA is predicted to have better passive permeability, and thus better biological efficacy.

Novel matrix metalloproteinase inhibitors: Generation of lead compounds by the in silico fragment-based approach.

K. Takahashi, M. Ikura, H. Habashita, M. Nishizaki, T. Sugiura, S. Yamamoto, S. Nakatani* [Minase Res Inst], K. Ogawa, H. Ohno, H. Nakai and M. Toda

Bioorg. Med. Chem. **13**, 4527-4543 (2005)

LUDI is used to identify the small fragment interacting with residues in the S1' pocket of MMP-1 through hydrogen bonds. Acetyl-L-alanyl-(*N*-methyl) amide was selected to link with another fragment, hydroxamic acid that interacted with catalytic zinc. This approach is used to discover the L-glutamic acid derivative to be a new type of matrix metalloproteinase inhibitor.

A

Quantitative Structure-Activity Relations

3D-QSAR study of bis-azaaromatic quaternary ammonium analogs at the blood-brain barrier choline transporter.

W.J. Geldenhuys, P.R. Lockman, T.H. Nguyen, C.J. Van der Schyf, P.A. Crooks, L.P. Dwoskin and D.D. Allen* [Texas Tech. Univ. Health Sci. Cent.]

Bioorg. Med. Chem. **13**, 4253-4261 (2005)

CoMFA and CoMSIA techniques are used to build the 3D-QSAR models for five bis-azaaromatic quaternary ammonium compounds for their affinity for the choline binding site on the blood-brain barrier (BBB)-choline transporter. The best-validated q^2 of CoMFA is 0.536 and r^2 is 0.818. CoMSIA hydrophobic cross-validated q^2 is 0.506 and r^2 is 0.804. This model is able to predict BBB-choline transporter affinity of hemicholinium-3.

Theoretical quantitative structure-activity relationships of flavone ligands interacting with cytochrome P450 1A1 and 1A2 isozymes.

F. Iori, R. da Fonseca, M. João Ramos and M.C. Menziani*[U degli Stu. di Modena e Reggio Emilia]

Bioorg. Med. Chem. **13**, 4366-4374 (2005)

QM calculations are used to obtain theoretical descriptors on isolated ligands in different media. MD simulations of ligand-enzyme complexes are used to obtain a quantitative rationalization of the inhibition of CYP1A2 and CYP1A2 by three series of flavonoids. QSAR studies are used to obtain predictive models through one-descriptor and mechanistic explanations are obtained for recognition and selectivity.

Quantitative Structure-Activity Relationships (cont'd)

Design and biological evaluation of phenyl-substituted analogs of β-phenylethylidenehydrazine.

B. Sowa, G. Rauw, A. Davood, A. Fassihi, E.E. Knaus and G.B. Baker* [Univ. of Alberta]

Bioorg. Med. Chem. **13**, 4389-4395 (2005)

A group of β-Phenylethylidenehydrazine analogs, with Me, OMe, Cl, F, and CF_3 substituents at the 2-, 3-, and 4 - positions of the phenyl ring are evaluated as inhibitors of GABA-T. Preliminary in vitro screening for GABA-T inhibition showed that all the analogs possessed activity against this enzyme, although substitution of CF_3 at the 2- and 4-positions caused reduced activity. 4-fluoro-β-phenylethylidenehydrazine inhibited GABA-T in further ex vivo investigation, elevate brain levels of GABA, and decrease levels of glutamine, similar to the profile observed previously for PEH.

A

Ligand-based assessment of factor Xa binding site flexibility via elaborate pharmacophore exploration and genetic algorithm-based QSAR modeling.

M.O. Taha* [Univ. of Jordan], A.M. Qandil, D.D. Zaki and M.A. AlDamen

Euro. J. Med. Chem. **40**, 701-727 (2005)

Four training subsets of wide structural diversity were selected from a total of 199 direct fXa inhibitors and CATALYST® is used to generate different fXa pharmacophoric hypotheses. In the first stage, high quality binding models were identified. In the second stage, the models were refined by applying variable-feature weight analysis to assess the relative significance of their features in the ligand-target affinity. The binding models were validated according to their coverage and predictive potential as 3D-QSAR models.

Assessing the reliability of a QSAR model's predictions.

Linnan He and Peter C. Jurs* [The Pennsylvania State Univ.]

J.Mol.Graph.Mod. **23**, 503-523 (2005)

Hierarchical clustering was developed and tested using a test dataset containing 322 organic compounds with fathead minnow acute aquatic toxicity as the activity of interest. This approach is to determine the relationship between the similarity of query compounds to the training set compounds of the QSAR model and the prediction accuracy given by that model. This relationship determination was achieved by comparing the results given by the two major components of the approach: objects clustering, and activity prediction.

Carbon Nanoparticles

Molecular-dynamics studies of bending mechanical properties of empty and C_{60}-filled carbon nanotubes under nanoindentation.

Y.-R. Jeng* [Natl Chung Cheng U], P.-C. Tsai, and T.-H. Fang

J. Chem. Phys. **122**, 22471301-22471308 (2005)

The strength of carbon nanotubes against indentation by an AFM probe was assessed with MD simulations. Bending strength is constant up to a 2.4-nm diameter, and then drops. Heat weakens the tubes. Filling with C_{60} strengthens the tubes at low temperature, but weakens at high temperature.

Self diffusion of argon in flexible, single wall, carbon nanotubes.

A. Marmier*[U Bath], H. Spohr, D.J. Cooke, S. Kerisit, J.P. Brodholt , P.B. Wilson , and S.C. Parker

Mol. Sim. **31**, 385-389 (2005)

Equilibrium molecular dynamics is used to calculate self-diffusivities of argon atoms diffusing through single wall carbon nanotubes. The effect of the rigidity/flexibility of the tube on the diffusivity is considered. The helicity and flexibility of the tubes have almost no noticeable influences. The size of the pore had a small effect, but the diffusivity depended essentially on the fluid loading.

1.2. *Biopolymers*

Threading and Fold Recognition

SCUD: Fast structure clustering of decoys using reference state to remove overall rotation.

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

J. Comp. Chem. **26,**1189-1192 (2005)

Clustering by RMSD from reference (rather than pairwise) enhances compute efficiency 9 fold with similar results, as shown by a study of 41 proteins with 2,000 decoys each. Structure ClUstering of Decoys, with an automatic cutoff value, is available at http://theory.med.buffalo.edu.

Protein Structure Prediction

Towards protein folding with evolutionary techniques.

F. Koskowski* [Christian-Albrechts-U] and B. Hartke

J. Comp. Chem. **26,**1169-1179 (2005)

An evolutionary secondary structure construction algorithm is successful at *ab initio* prediction (to the extent that the force field is adequate).

Comparative or Homology Modeling

Understanding human 15-hydroxyprostaglandin dehydrogenase binding with NAD^+ and PGE_2 by homology modeling, docking and molecular dynamics simulation.

A. Hamza, H. Cho, H.-Hsiung Tai* [U Kentucky], and C.-Guo Zhan

Bioorg. Med. Chem. **13**, 4544 -4551 (2005)

Homology modeling, molecular docking, and MD simulations are used to determine human 15-hydroxyprostaglandin dehydrogenase (15-PGDH) binding with its NAD^+ cofactor and prostaglandin E2 (PGE_2) substrate. The computational studies lead to a 3-D model of the entire 15-PGDH-NAD^+-PGE_2 complex, explained the binding of PGE_2 with 15-PGDH for the first time. The proposed 3D model of the 15-PGDH-NAD+-PGE2 complex is useful for future rational design of novel inhibitors of 15-PGDH.

Peptide Conformational Analysis

Structure and stability of β-pleated sheets.

A. Perczel* [Eötvös U], Z. Gáspári, and I.G. Csizmadia

J. Comp. Chem. **26,**1155-1168 (2005)

Ab initio calculations show that 1) the 14-atom Hbond ring is more stable than the 10-atom ring in antiparallel sheets; 2) antiparallel is more stable than parallel; and 3) sheets are more stable than hairpins.

Protein Folding

Combinatorial pattern discovery approach for the folding trajectory analysis of a β-hairpin.

L. Parida [IBM] and R. Zhou [IBM]

PloS Comp. Biol. **1**, 32-40 (2005)

An algorithm for analyzing a protein folding trajectory reproduces previous results and predicts a new critical folding transition for a β-hairpin.

Protein Folding (cont'd)

Simulation and experiment conspire to reveal cryptic intermediates and a slide from the nucleation-condensation to framework mechanism of folding.

G.W.N. White, S. Gianni, J.G. Grossmann, P. Jemth, A.R. Fersht* [MRC], and V. Daggett* [U Washington]

J. Mol. Biol. **349**, 757-775 (2005)

MD simulations of protein folding is coupled with protein engineering experiments to elucidate the folding pathway of c-Myb as utilizing a mixed folding mechanism involving both classical framework and nucleation-condensation mechanisms.

Theoretical model of prion propagation: A misfolded protein induces misfolding.

E. Maiolepsza* [Warsaw U], M. Boniecki, A. Kolinski and Lucjan Piela

PNAS **102,** 7835-7840 (2005)

A theoretical model of the molecular mechanism of conformational disease is proposed, in which a metastable (or misfolded) form of a protein induces a similar misfolding of another protein molecule. A number of amino acid sequences composed of 32 aa are designed that fold rapidly into a well-defined native-like α-helical conformation. Simulations were done by using a reduced protein model and the replica exchange Monte Carlo sampling procedure.

Protein Design and Engineering

Adaptation of a fast Fourier transform-based docking algorithm for protein design.

P.-S. Huang* [Calif Inst Tech], J.J. Love, and S.L. Mayo

J. Comp. Chem. **26,**1222-1232 (2005)

Homodimer interfaces with C2 symmetry can be designed with up to 70% success rate using an FFT-based hydrophobicity analysis of the putative interdimer surface.

Hydroxyl groups in the ββ sandwich of metallo-β-lactamases favor enzyme activity: A computational protein design study.

P. Oelschlaeger and S.L. Mayo* [Caltech]

J. Mol. Biol. **349**, 395-401 (2005)

Protein design calculations successfully find mutants of IMP-1 that experimentally show improved catalytic efficiency toward a range of substrates. This is particularly interesting since *in vitro* evolution did not find mutants with improved enzymatic activity towards one of the substrates, IMP.

Protein Hydration

Protein boson peak originated from hydration-related multiple minima energy landscape.

Y. Joti, A. Kitai* [U Tokyo], and N. Go

J. Amer. Chem. Soc. **127**, 8705-8709 (2005)

MD simulations on lysozyme as a function of temperature and using methods ranging from in-vacuo, to generalized Born to explicit solvent simulation aim to explain the boson peak. The results, which only show a boson peak in simulations under 200K when explicit solvent is applied, suggest that extra local minima due to the water are the origin of the peak.

Protein Folding (cont'd)

Molecular dynamics simulations for selection of kinetic hydrate inhibitors.

B. Kvamme* [U Bergen], T. Kuznetsova, and K. Aasoldsen.

J. Mol. Graph. Mod. **23**, 524-536 (2005)

MD simulations are used to test several kinetic inhibitors in a multiphase water-hydrate system with rigid hydrate interface. PVCap outperforms PVP as a kinetic hydrate inhibitor, as supported by experimental data. Numerical experiments are done as a valuable tool for selecting kinetic inhibitors as well as to provide insight into the mechanisms of kinetic inhibition and hydrate melting and reformation.

Protein Dynamics

Coupling between lysozyme and glycerol dynamics: Microscopic insights from molecular-dynamics simulations.

T.E. Dirama, G.A. Carri, and A.P. Sokolov

J. Chem. Phys. **122**, 24491001-24491010 (2005)

The dynamical effects of glycerol, a common thermoprotectant, on lysosyme include increased effective viscosity near the protein and coupling through hydrogen bond networks. The surface residues are more coupled to solvent motions than interior residues.

Simulation studies of amide I IR absorption and two-dimensional IR spectra of β-hairpins in liquid water.

S. Hahn, S. Ham, and M. Cho* [Korea U]

J. Phys. Chem. B **109**, 11789-11801 (2005)

MD simulation and experiment are performed to give insight into amide vibrations.

Langevin model of the temperature and hydration dependence of protein vibrational dynamics.

K. Moritsugu and J. C. Smith* [U Heidelberg]

J. Phys. Chem. B **109**, 12182-12194 (2005)

MD simulations on myoglobin are analyzed using a Langevin model of the vibrational dynamics and compared to standard harmonic normal mode analysis.

Ligand Binding

Absolute free energies of binding of peptide analogs to the HIV-1 protease from molecular dynamics simulations.

C. Bartels* [Novartis], A. Widmer, and C. Ehrhardt

J. Comp. Chem. **26,**1294-1305 (2005)

Peptide binding to HIV-1 protease was predicted accurately with MD using PBSA salvation. To get sufficient affinity, it is necessary to use 8 mol^{-1} K^{-1} $Å^{-2}$ for the surface tension parameter.

Validation and use of the MM-PBSA approach for drug discovery.

B. Kuhn* [Roche], P. Gerber, T. Schulz-Gasch, and M. Stahl

J. Med. Chem. **48**, 4040-4048 (2005)

Applying MM/PBSA to a set of protein-ligand complexes using a single minimized conformation appears to perform as well, and sometimes better, than MM/PBSA using a MD ensemble. Also, binders that differ by 2-3 orders of magnitude in IC50 are found to be distinguishable by MM/PBSA.

Ligand Binding (cont'd)

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The PDBbind database: Methodologies and updates.

R. Wang, X. Fang, Y. Lu, C-Y Yang, and S. Wang* [U Michigan]

J. Med. Chem. **48**, 4111-4119 (2005)

An update to PDBbind includes 1622 protein-ligand complexes with annotated affinities, and a 900 complex subset that is useful for docking studies.

Rapid computational identification of the targets of protein kinase inhibitors.

W.M. Rockey and A.H. Elcock* [U Iowa]

J. Med. Chem. **48**, 4138-4152 (2005)

A method that uses a simple empirical energy function and explicit sampling of side chain rotamers is fast. Application to a full matrix of seven compounds against 20 kinases suggests that the method can approximately discriminate many targets that the compounds potently inhibit.

A

Unveiling the full potential of flexible receptor docking using multiple crystallographic structures.

X. Barril* [Vernalis] and S.D. Morley

J. Med. Chem. **48**, 4432-4443 (2005)

A study of docking to 34 CDK2 and 57 HSP90 receptor crystal structures finds that flexible receptor docking yields binding mode predictions on par with native receptor docking, and thus can be useful in predicting binding modes. For binding energy and enrichment applications, however, using multiple receptor structures results in worse results.

The role of the peripheral anionic site and cation-π interactions in the ligand penetration of the human AChE gorge.

D. Branduardi, F. L. Gervasio* [ETH], A. Cavalli* [U Bologna], M. Recanatini, and M. Parrinello

J. Amer. Chem. Soc. **127**, 9147-9155 (2005)

The metadynamics molecular dynamics method is applied to understand tetramethylammonium interaction interaction with AChE. Metadynamics appears to speed up activated reactions and facilitate reconstruction of the free energy surface via the addition of a Gaussian repulsive potential that loosely remembers the MD history along chosen collective variables.

Elucidation of the Na^+, K^+-ATPase digitalis binding site.

S.M. Keenan, R.K. DeLisle, W.J. Welsh* [Robert Wood Johnson Med School], S. Paula and William J. Ball, Jr.

J. Mol. Graph. Mod. **23**, 465-475 (2005)

The binding mode of Digoxin and several analogs to the Na+, K+-ATPase was proposed. 3D-structural model of the extracellular loop regions of the catalytic α1-subunit of the digitalis-sensitive sheep Na+, K+-ATPase was constructed from an E1Ca2+ conformation of the SERCA1a. A consensus orientation for digitalis binding was inferred from the in silico docking of a series of steroid-based cardiotonic compounds. Analyses of species-specific enzyme affinities for ouabain validate the model and suggest a detailed model of the digitalis binding site.

Ligand Binding (cont'd)

Predictive Bayesian neural network models of MHC class II peptide binding.

F.R. Burden and D.A. Winkler* [Monash U]

J. Mol. Graph. Mod. **23**, 481-489 (2005)

Robust models were obtained with near identical statistics for multiple training runs. Statistical tests and area under the Receiver-Operating-Characteristic graphs are used to predict the models. Most of the models gave training AROC values close to 1.0 and test set AROC values >0.8. Both amino acid indicator variables and property-based descriptors were used to generate models for MHC class II-binding of peptides. The property-based descriptors were more parsimonious than the indicator variable descriptors.

Protein structure similarity clustering (PSSC) and natural product structure as inspiration sources for drug development and chemical genomics.

F.J. Dekker, M.A. Koch, and H. Waldmann*
[Max-Planck Inst Mol Physiol]

Curr. Opi. Chem. Biol. **9**,232-239 (2005)

A novel strategy is developed to make the use of structural conservatism found in protein domain architecture and natural product inspired compound library design. Domains and proteins identified as structurally similar in their ligand-sensing cores are grouped in a protein structure similarity cluster. This strategy is applicable for compound library design, providing enhanced hit rates in small compound libraries for structurally similar proteins.

Construction of a virtual combinatorial library using SMILES strings to discover potential structure-diverse PPAR modulators.

C. Liao* [Res Inst of Tsinghua U], B. Liu, L. Shi,
J. Zhou and Xian-Ping Lu

Euro. J. Med.Chem. **40**, 632-640 (2005)

SMILES strings are used to construct a virtual combinatorial library containing 1,226,625 compounds. DOCK 4.0 is used to dock PPARγ to identify new chemical entities that are potential drug leads against type 2 diabetes and other metabolic diseases.

Protein-Protein Interactions

A model for the interaction between plant GAPN and 14-3-3ζ using protein-protein docking calculations, electrostatic potentials and kinetics.

Diego M. Bustos and Alberto A. Iglesias*
[Lab Enzimolog Mol]

J.Mol.Graph.Mod. **23**, 490-502 (2005)

The crystal structure of a 14-3-3-target protein complex was determined for serotonin *N*-acetyltransferase. The BiGGER program was used for initial dockings, allows an exhaustive search of translational and rotational space. The binding configurations is predicted by attractive electrostatic interactions.

Membrane Proteins and Lipid-Peptide Interactions

Imaging α-hemolysin with molecular dynamics: Ionic conductance, osmotic permeability, and the electrostatic potential map

A. Aksimentiev and K. Schulten*
[U Illinois Urbana-Champaign]

Biophys. J. **88,** 3745-3761 (2005)

The single channel current in a 300,000-atom system was simulated with an applied voltage. Conductance, electroosmosis, and His-titration gating were accurately predicted.

Membrane Protein Lipid-Peptide Interactions (cont'd)

Molecular dynamics simulations of C_2F_6 effects on gramicidin A: Implications of the mechanisms of general anesthesia.

Z. Liu* [U Pittsburgh], Y. Xu, and P. Tang

Biophys. J. **88,** 3784-3791 (2005)

MD simulations show that the global changes in gramicidin channel dynamics that occur with halothane is missing in the presence of the similar but nonanesthetic compound, hexafluoroethane.

Normal mode analysis suggests a quaternary twist model for the nicotinic receptor gating mechanism.

A. Taly, M. Delarue, T. Grutter, M. Nilges, N. Le Novère, P.-J. Corringer, and J.-P. Changeux* [Inst Pasteur]

Biophys. J. **88,** 3954-3965 (2005)

A model for the acetylcholine receptor channel based has a lowest frequency mode that oscillates between a wide open channel and a closed channel. Opposing twists occur in extracellular and transmembrane domains.

Electric-field-controlled water and ion permeation of a hydrophobic nanopore.

J. Dzubiella* [U Calif San Diego] and J.-P. Hansen

J. Chem. Phys. **122**, 23470601-23470614 (2005)

Water fails to fill a model hydrophobic channel in a membrane unless a strong potential across the membrane polarizes the water within the entryway, which then is prone to enter the pore. The mechanism is proposed as a possible basis for voltage-gating of channels.

Insights into the recognition and association of transmembrane α-helices. The free energy of α-helix dimerization in glycophorin A.

J. Henin, A. Pohorille, and C. Chipot* [CNRS]

J. Amer. Chem. Soc. **127**, 8478-8484 (2005)

The adaptive biasing force method which integrates the average force acting on the reaction coordinate (in this case the distance between the centers of mass of the helices) is applied to estimate the PMF for the association of the two α-helices in glycophorin A in a water/dodecane (model bilayer) system. A two step association process is suggested.

Molecular dynamics simulations of unsaturated lipid bilayers: Effects of varying the numbers of double bonds.

M.T. Hyvönen* [Helsinki U Tech] and P.T. Kovanen

Euro.Biophys. J. **34**, 294-305 (2005)

MD simulations are used to study the effects of unsaturation on the nanosecond-scale structural and dynamic properties of the phosphatidylcholine bilayer. Some problems occur in the CHARMM force field of the lipids when applied in a constant pressure ensemble. The presence of double bonds in the *sn*-2 chains considerably reduces the order parameters of the CH bonds. The double bond region of tetraunsaturated chains is shown to span all the way from the bilayer centre to the head group region.

Protein-Nucleic Acid Interactions

Docking simulation with a purine nucleoside specific homology model of deoxycytidine kinase, a target enzyme for anticancer and antiviral therapy.

J. Johnsamuel* [Ohio State U], S. Eriksson, M. Oliveira and W. Tjarks

Bioorg. Med. Chem. **13**, 4160-4167 (2005)

Human deoxycytidine kinase (dCKm) is essential for computer aided molecular design of novel anticancer and antiviral drugs. Comparative docking simulations of deoxycytidine (dC), cytidine (Cyd), AraC, CdA, deoxyadenosine (dA), and deoxyguanosine (dG) with dCKm and dCKc were carried out using the FlexX™ docking program. The active site of dCKm appeared to be more adapted to bind purine nucleosides than the pyrimidine nucleosides.

Proteins and Surfaces

Topography of the free-energy landscape probed via mechanical unfolding of proteins.

S. Kirmizialtin, L. Huang, and D.E. Makarov*
[U Texas Austin]

J. Chem. Phys. **122**, 23491501-23491512 (2005)

Simulations of stretching of ubiquitin show the tension between the extending force and the elastic recoil of the protein, and that sharp stretches are followed by diffusive renaturation producing the so-called slow phase.

Lipids and Surfactants

Lipid bilayer perturbations around a transmembrane nanotube: A coarse grain molecular dynamics study.

S.O. Nielsen* [U Penn], B. Ensing, V. Ortiz, P.B. Moore, and M.L. Klein

Biophys. J. **88,** 3822-3828 (2005)

Bilayer thickness is perturbed around a hydrophobically mismatched nanotube and the nanotube tilts, but not enough to completely compensate for the mismatch according to coarse-grained simulations.

Molecular dynamics simulations and ^{2}H NMR study of the GalCer/DPPG lipid bilayer.

T. Zaraiskaya and K.R. Jeffrey* [U Guelph]

Biophys. J. **88,** 4017-4031 (2005)

In closely packed bilayers, hydrogen bonding between hydroxyl groups from opposing GalCer sugar headgroups appear to be responsible for adhesion energies.

Membrane electroporation: A molecular dynamics simulation.

M. Tarek* [U Henri-Poincaré]

Biophys. J. **88,** 4045-4053 (2005)

Explicit solvent simulations with a bare bilayer, a nanochannel, or DNA in the bulk show that 1V/nm produces water wires in the bilayer that are excluded near the nanochannel and that facilitate the entry of DNA into the bilayer.

Direct computer simulation of water-mediated force between supported phospholipid membranes.

A. Pertsin* [U Heidelberg], D. Platonov, and M. Grunze

J. Chem. Phys. **122**, 24470801-24470809 (2005)

Grand canonical MC with atomistic DLPC and TIP4 water is used to decompose the energy terms responsible for forces between two supported, closely apposed bilayers. Although it was hard to get sufficient conformational sampling, it was clear that hydration forces and bilayer-bilayer interactions both contribute.

Lipids and Surfactants (cont'd)

Molecular dynamics investigation of the structural properties of phosphatidylethanolamine lipid bilayers.

F. Suits* [IBM], M.C. Pitman, and S.E. Feller

J. Chem. Phys. **122**, 24471401-24471409 (2005)

A well-equilibrated SOPE bilayer shows much more hydrogen bonding between headgroup amine and phosphate groups than is found in PC bilayers. A companion paper compares dynamical properties from the simulations to NMR observables. The computed lateral diffusion coefficient of the lipids is a slightly low, but respectable $4x10^{-8}$ cm^2/s.

Multiscale coupling of mesoscopic- and atomistic-level lipid bilayer simulations.

R. Chang, G.S. Ayton, and G.A. Voth* [U Utah]

J. Chem. Phys. **122**, 24471601-24471612 (2005)

Large-scale (10^4 nm^2) mesoscopic simulations are used to derive boundary conditions for atomistic DMPC simulations, which in turn provide structural parameters for the mesoscopic system. The combination allows accurate estimation of lateral diffusion coefficients and lipid dipole relaxations, which are very system-size dependent.

Effect of chain length and asymmetry on material properties of bilayer membranes.

G. Illya* [Max Planck], R. Lipowsky, and J. C. Shillcock

J. Chem. Phys. **122**, 24490101-24490106 (2005)

According to mesoscopic model simulations (dissipative dynamics), the experimentally observed lack of dependence of bending and stretch moduli on lipid chain length would require a concomitant increase in head group interaction. The area stretch modulus is reduced in bilayers with asymmetric tails.

Asymmetry of lipid bilayers induced by monovalent salt: Atomistic molecular-dynamics study.

A.A. Gurtovenko* [Helsinkin U Tech and Russian Acad Sci]

J. Chem. Phys. **122**, 24490201-24490210 (2005)

If there is NaCl on one side of a PC bilayer but not the other, the head groups stand up taller due to interactions between choline and extramembranous Cl^-, and the carbonyl regions of adjacent molecules are bridged by Na^+ ions, producing coupled lateral motions. The charge imbalance is sufficient to produce an 85-mV membrane potential.

Molecular dynamics simulations of phospholipids bilayers: Influence of artificial periodicity, system size, and simulation time.

A. H. de Vries* [ETH], I. Chandrasekhar,
W. F. Van Gunsteren, and P. H. Hunenberger

J. Phys. Chem. B **109**, 11643-11652 (2005)

Hydrated DPPC bilayers of varying sizes are studied in MD simulation to give insight into finite size effects. Short time scale properties (< ns) were shown to become reasonable as the size of the lipid bilayer in the unit cell increased from 2 lipids to 64 lipid molecules or beyond. The smaller systems suffered from surface tension, electron density and bias orientation deficiencies.

Carbohydrates

A coarse-grained molecular model for glycosaminoglycans: Application to chondroitin, chondroitin sulfate, and hyaluronic acid.

M. Bathe, G.C. Rutledge, A.J. Grodzinsky,
and B. Tidor* [Mass Inst Tech]

Biophys. J. **88,** 3870-3887 (2005)

A coarse-grained model of glycosaminoglycans based on disaccharide building blocks was carried out to assess compressibility and titration of cartilage ground substance. Sulfonation at position 4 stiffens more than at position 6.

Carbohydrates (cont'd)

How homogeneous are the trehalose, maltose, and sucrose water solutions? An insight from molecular dynamics simulations.

A. Lerbret* [U Lille], P. Bordat, F. Affouard, M. Descamps, and F. Migliardo

J. Phys. Chem. B **109**, 11046-11057 (2005)

MD simulations with DL_POLY are applied to various concentrations of sugar solution. Trehalose is shown to bind more water than either sucrose or maltose, which in turn more greatly alters its properties. The larger clusters that form suggest that trehalose would be a better sugar to add to reduce ice formation and desiccation stresses.

1.3. Surfaces, Catalysts, and Material Subjects

Simulating adsorption of *n*-heptane in the Pt/Al_2O_3 model: Influence of platinum.

B. Szyja* [Wrocław U Tech] and J. Szczygieł

J. Mol. Graph. Mod. **23**, 476-480 (2005)

UFF and CVFF forcefield methods are used to describe relevant interactions of *n*-heptane adsorption on the Pt/γ-Al_2O_3 catalyst. Pt was found to exert an advantageous effect on the adsorption of *n*-heptane. The number of adsorbed molecules was related to the content of the noble metal, and the relation was directly proportional when temperature and pressure were constant. The contribution of Pt was most distinct at 573 K and 100 kPa.

A computational study of the effect of Li-K solid solutions on the structures and stabilities of layered silicate materials - An application of the use of Condor pools in molecular simulation.

Z. Du*, N.H. de Leeuw , R. Grau-Crespo, P.B. Wilson, J.P. Brodholt, M. Calleja, and M.T. Dove [U London]

Mol. Sim. **31**, 339-347 (2005)

The structures and stabilities of Li-K solid solutions of three different disilicate structures were investigated by computer modelling techniques. A new program was developed based on symmetry arguments to identify identical configurations and hence eliminate unnecessary duplication of calculations. The results showed that in the wide range of Li-K solid solutions, the mixed-cationic $KLiSi_2O_5$ material retains its original structure when the composition was varied, where six-membered rings of silica tetrahedra are linked to form continuous channels throughout the structure.

2. METHODOLOGY

Potentials and Parameters

Representation of Zn(II) complexes in polarizable molecular mechanics. Further refinements of the electrostatic and short-range contributions. Comparisons with parallel ab initio computations.

N. Gresh* [IFR Biomédicale, NIEHS], J.-P. Piquemal, and M. Krauss

J. Comp. Chem. **26,**1113-1130 (2005)

Energies predicted by the SIBFA semi-empirical approach to molecular mechanics have 3% accuracy, even though components have up to 1200 kcal/mol.

Potentials and Parameters (cont'd)

Comparing polarizable force fields to *ab initio* calculations reveals nonclassical effects in condensed phases.

R. Chelli* [U Firenze], V. Schettino, and P. Procacci

J. Chem. Phys. **122**, 23410701-23410707 (2005)

Although polarizable force fields neglect many-body exchange and polarization and therefore overestimate polarization energy in a condensed phase (like a bifurcated water chain), they also neglect charge transfer in hydrogen bonds, which underestimates polarization. Bulk water suffers more from the latter effect.

Validation of intermolecular pair potential model of SiH_4: Molecular-dynamics simulation for saturated liquid density and thermal transport properties.

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

J. Chem. Phys. **122**, 23450101-23450108 (2005)

An anisotropic force field for SiH_4 with Buckingham VDW give average density errors of ~3% between 100 K and 225 K (compared to 10% for an LJ VDW force field) and 12-14% errors for sheer viscosity and thermal conductivity. The thermal conductivity is greatly enhanced by rotational energy transfer, as shown by comparison to a united atom model.

The elasticity of α-helices.

S. Choe and S.X. Sun* [Johns Hopkins U]

J. Chem. Phys. **122**, 24491201-24491209 (2005)

The bending modulus (persistence length) of most α-helices, with or without explicit water, is ~100 nm according to MD simulations. Mechanical properties are well reproduced by an elastic isotropic rod, which may be helpful for mesoscopic approaches.

Validation of the 53A6 GROMOS force field.

C. Oostenbrink, T.A. Soares, N.F. A. van der Vegt, and W.F. van Gunsteren* [Swiss Fed Inst Tech]

Euro. Biophys. J. **34**, 273-284 (2005)

The new 53A6 GROMOS force field was validated with three test cases. Simulations were applied to analyze the 129 residue protein hen egg-white lysozyme, the DNA dodecamer d$(CGCGAATTCGCG)_2$, and a proteinogenic β_3-dodecapeptide. The new parameter set performs as well as the previous parameter sets in terms of protein (45A3) and DNA (45A4) stability, and it is better at describing the folding-unfolding balance of the peptide.

Solvation Energy

Building cavities in a fluid of spherical or rod-like particles: A contribution to the solvation free energy in isotropic and anisotropic polarizable continuum model.

C. Benzi* [U Federico II], M. Cossi, R. Improta, and V. Barone

J. Comp. Chem. **26,**1096-1105 (2005)

The cavitation free energy in the Polarizable Continuum Model can be computed using spherocylinders with anisotropic fields and gives reasonable accuracy.

!

Solving the Poisson-Boltzmann equation with the specialized computer chip MD-GRAPE-2.

S. Höfinger* [Novartis]

J. Comp. Chem. **26,**1148-1154 (2005)

PB calculations are sped up by 15- to 40-fold for peptides and proteins with the Boundary Element Method implemented on MD-GRAPE-2.

Electrostatics and Titration

Proton binding to proteins: A free-energy component analysis using a dielectric continuum model.

G. Archontis* [U Cyprus] and T. Simonson* [Ecole Polytech]

Biophys. J. **88,** 3888-3904 (2005)

For thioredoxin as a test system, a continuum theory that averages over conformations for titration endpoints yields accurate pKa estimates, as well as solvation and other parameters that coincide with explicit solvent MD. Standard PB estimates do not give balanced estimates.

Computation of electrostatic forces between solvated molecules determined by the Poisson–Boltzmann equation using a boundary element method.

B. Lu* [U Calif San Diego], D. Zhang, and J.A. McCammon

J. Chem. Phys. **122**, 21410201-21410207 (2005)

A novel approach to the linearized PB that side steps the hypersingularity found in the direct boundary element method. It can be used in MD simulations for several interacting particles.

Monte-Carlo Simulation

A simulation method for the calculation of chemical potentials in small, inhomogeneous, and dense systems.

A.V. Neimark* [Textile Res Inst] and A. Vishnyakov

J. Chem. Phys. **122**, 23410801-23410811 (2005)

This paper describes the use of a gauge system connected to the central system. Changes in density in the gauge system reflect the chemical potential in the central system. The method bridges the gap between canonical ensemble and grand canonical ensemble statistics, which is problematic for small systems.

Free Energy Methods

Robust and accurate method for free-energy calculation of charged molecular systems.

J. Anwar and D.M. Heyes* [U Surrey]

J. Chem. Phys. **122**, 22411701- 22411707 (2005)

With a damping potential in the Ewald summation, a robust approach to creation/annihilation of particles is possible, which allows accurate free energy perturbations.

QM/MM

Long-range electrostatic interactions in hybrid quantum and molecular mechanical dynamics using a lattice summation approach.

F. Dehez, M.T.C. Martins-Costa, D. Rinaldi, and C. Millot* [U Henri Poincaré-Nancy]

J. Chem. Phys. **122**, 23450301-23450311 (2005)

How is the QM component of a QM/MM system handled in Ewald summation? Mulliken charges are efficient and sufficiently accurate for accurate salvation energy and diffusion coefficient calculations based on a test with QM Cl^- in MM water.

A quantum mechanical polarizable force field for biomolecular interactions.

A.G. Donchev, V.D. Ozrin, M.V. Subbotin, O.V. Tarasov, and V.I. Tarasov* [Force Field Lab]

PNAS **102,** 7829-7834 (2005)

Quantum mechanical polarizable force field (QMPFF) is introduced, fitted solely to QM data at the MP2/aTZ(-hp) level. The functional form of interaction energy parallels quantum mechanics by including electrostatic, exchange, induction, and dispersion terms. QMPFF is much more efficient than *ab initio* QM and is optimized for the accurate simulation of biomolecular systems and the design of drugs.

Protein Folding

!

Relating kinetic rates and local energetic roughness by accelerated molecular-dynamics simulations.

D. Hamelberg* [U Calif San Diego], T. Shen, and J.A. McCammon

J. Chem. Phys. **122**, 24110301-24110304 (2005)

The accelerated MD method derives from Voter's surface flattening method, but uses a fixed potential energy threshold and scale factor to modify the potential in a way that allows continuity at the threshold. This avoids expensive calculation of the Hessian at each time step. In deriving the effective time scale for this simpler approach, the authors also discovered how to correctly ascertain the real energetic roughness. Here, the *cis-trans* isomerization of Ser-Pro (>ms) is converted to <ns by application of the ΔV function to the ω dihedral only.

Ligand Docking

Complexes of thiomandelate and captopril mercaptocarboxylate inhibitors to metallo--lactamase by polarizable molecular mechanics. Validation on model binding sites by quantum chemistry.

J. Antony, J.-P. Piquemal, and N. Gresh* [IFR Biomédicale, NIEHS]

J. Comp. Chem. **26,**1131-1147 (2005)

Interactions between captopril and bacterial lactamase are similar with SIBFA and *ab intio* calculations.

New and fast statistical-thermodynamic method for computation of protein-ligand binding entropy substantially improves docking accuracy.

A.M. Ruvinsky* [Algodign] and A.V. Kozintsev

J. Comp. Chem. **26,**1089-1095 (2005)

If one properly includes loss of translation, rotational and torsional entropy changes for a ligand upon binding, AutoDock accuracy can be increased by 10-21%.

Representing receptor flexibility in ligand docking through relevant normal modes.

C.N. Cavasotto* [Molsoft], J.A. Kovacs, and R.A. Abagyan

J. Amer. Chem. Soc. **127**, 9632-9640 (2005)

A normal mode approach is incorporated to enable ligand flexibility in a ligand docking procedure.

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