Results

MOLECULAR MODELING & COMPUTATIONAL CHEMISTRY

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About 110 papers from 20 journals are cited.

Editorial and News

In this issue, several articles focused on mesoscopic modeling of lipid layers with an emphasis on their mechanical properties.

Some of the articles related to the coarse-graining of macromolecules and material science are intersting. I would call your attention on few highlighted articles, particularly in the Methodology section related to potentials and parameters.

R.Nageswar, Editor

1. APPLICATIONS

1.1. *Small Molecules*

General and Model Systems

How well can coarse-grained models of real polymers describe their structure? The case of polybutadiene.

Leonid Yelash* [Johannes-Gutenberg Univ.], Marcus Müller, Wolfgang Paul, and Kurt Binder

J.Chem. Theor.and Comp. **2**, 588-597 (2006)

United atom force field model of polybutadiene based MD simulation data is used to investigate the coarse-graining of chemical structure of macromolecules. The influence of degree of coarse-graining on the structure functions is studied. The results are compared to MC simulations of the corresponding coarse-grained bead-spring model and Chen-Kreglewski potential for chain molecules.

The extent of cooperativity of protein motions observed with elastic network models is similar for atomic and coarser-grained models.

T.Z. Sen, Yaping Feng, J.V. Garcia,
A. Kloczkowski, and R.L. Jernigan* [Iowa State Univ.]

J.Chem. Theor. and Comp. **2**, 696-704 (2006)

The applicability of elastic network models over a broader range of representational scales is compared. Normal mode analysis is applied for multiple scales on a high-resolution protein data set using various cutoff radii to define the residues considered the extent of cooperativity of their motions. The results showed that atomic level elastic network models provide an improved representation for the collective motions of proteins compared to the coarse-grained models.

Water and Solvation

Simulation of phase separation in alcohol/water mixtures using two-body force field and standard molecular dynamics.

E.S. Ferrari, R.C. Burton , R.J. Davey* [The Univ. of Manchester], A. Gavezzotti

J.Comp. Chem. **27,** 1211-1219 (2006)

MD simulations are carried out on pure alcohols and alcohol/water mixtures. All-atom force field with Lennard-Jones potentials are used for mixtures by developing combination rules with the TIP3P water model. The results showed the ability of a molecular dynamics simulation with optimized force field, to simulate and, to a certain extent, predict the properties of binary mixtures.

MMCC Results
R.Nageswar, Editor
8013 Los Sabalos Street
San Diego, CA 92126
Tel. (858) 663-0162
e-mail: *drnageswar@yahoo.com*

R.Nageswar,Ph.D.
RR Labs Inc.,8013 Los Sabalso St.
San Diego, CA 92126
Editors Emeritus: Bruce Gelin, Ph.D.
David Busath,M.D.
Dr. Gelin was founder of MMCC Results and edited volumes 1-6.
Dr. David Busath edited volumes 7-14

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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 [**!**].

Water and Solvation (cont'd)

Fast relaxation dynamics of the cardiotonic drug milrinone in water solutions.

M. El-Kemary, J.A. Organero, and A. Douhal* [Univ. de Castilla-La Mancha]

J. Med. Chem., **49** (11), 3086 -3091, 2006

The fast relaxation dynamics of 1,6-dihydro-2-methyl-6-oxo-3,4'-bipyridine-5-carbonitrile is characterized in water solutions at different pH. B3LYP with 6-31+G** level calculations showed that in a water cavity, K is more stable than the enol form by 7 kcal/mol, and the ICT could take place within the pyridone moiety.

Gd(III) Polyaminocarboxylate chelate: Realistic many-body molecular dynamics simulations for molecular imaging applications.

Carine Clavaguéra, Emmanuelle Sansot, Florent Calvo, and Jean-Pierre Dognon* [Univ. Paul Sabatier]

J. Phys. Chem. B. **110** (26), 12848-12851 (2006)

MD simulations are used to study the polyaminocarboxylate complexes of gadolinium (III) ion in water. The results providing coordination numbers and average residence times in quantitative agreement with available experimental data. A theoretical analysis, based on fitting a fluctuating charges model on ab initio data, indicates that charge transfer between the ion and the ligand is significant.

Elastic bag model for molecular dynamics simulations of solvated systems: Application to liquid water and solvated peptides.

Yuhui Li, Goran Krilov, and B.J. Berne* [Columbia Univ.]

J. Phys. Chem. B. **110** (26), 13256-13263 (2006)

The extended fluctuating elastic boundary (FEB) model is applied for the simulation of bulk water and solvated alanine dipeptide. Both the confining potential and boundary particle interaction functions are modified to preserve the structural integrity of the boundary and prevent the leakage of the solute-solvent system through the boundary. The applicability of this model to biomolecular simulations is investigated through the analysis of conformational population distribution of solvated alanine dipeptide.

Medicinal Chemistry and Drug Design

A!
New leads for selective GSK-3 inhibition: Pharmacophore mapping and virtual screening studies.

D.S. Patel and P.V. Bharatam*[NIPER]

*J.Comp. Aided Mol.Design.***20**, 55-66 (2006)

A pharmacophore mapping strategy is employed to identify new leads for selective GSK-3 inhibition. Distance comparison method (DISCO) is used to generate a pharmacophore map to show selective GSK-3 inhibition. The derived pharmacophore map is validated using (i) important interactions involved in selective GSK-3 inhibitions, and (ii) an in-house database containing different classes of GSK-3 selective, non-selective and inactive molecules. FlexX based molecular docking study is carried out for final screening.

Anticancer thiopyrano[2,3-*d*][1,3]thiazol-2-ones with norbornane moiety. Synthesis, cytotoxicity, physico-chemical properties, and computational studies.

Roman Lesyk* [Danylo Halytsky Lviv Nati. Medical Univ.], Borys Zimenkovsky, Dmytro Atamanyuk, Frank Jensen, Katarzyna Kieć-Kononowicz and Andrzej Gzella

Bioorg. Med. Chem. **14**, 5230-5240 (2006)

COMPARE analyses of differential growth inhibition patterns of compounds at the GI_{50} level showed high correlations with some of the antitubulin agents. The lipophilicity of the compounds was studied by RP-TLC and found to correlate well with calculated log *P* values. Docking and structure-activity relationship studies produced seven QSAR models with 2 or 3 variables, with correlation coefficients $r^2 > 0.9$ and leave-one-out cross-validation correlation coefficients, $q^2 > 0.8$.

Medicinal Chemistry and Drug Design (cont'd)

Synthesis and biological evaluation of linear phenylethynylbenzenesulfonamide regioisomers as cyclooxygenase-1/-2 (COX-1/-2) inhibitors.

R. Anana, P.N. Praveen Rao, Qiao-Hong Chen and E.E. Knaus* [Univ. of Alberta]

Bioorg. Med. Chem. **14**, 5259-5265 (2006)

Molecular modeling studies showed that the *meta*-SO_2NH_2 COX-2 pharmacophore is inserted inside the COX-2 secondary pocket (Arg-513, Phe-518, Val-523, and His-90). Docking of 3-(2-phenylethynyl)benzene-sulfonamide within the COX-1 binding site showed that the *meta*-SO_2NH_2 pharmacophore is unable to interact with the respective amino acid residues in COX-1 that correspond to those near the secondary pocket in COX-2 due to the presence of the larger Ile-523 in COX-1 that replaces Val-523 in COX-2.

Heterocyclic analogs of benzanilide derivatives as potassium channel activators. IX.

V. Calderone*[Univ. of Pisa], F.L. Fiamingo, I. Giorgi, M. Leonardi, Oreste Livi, A. Martelli and E. Martinotti

Euro. J. Med. Chem. **41**, 761-767 (2006)

The pharmacological results are provided the structural requirements, needed for a satisfactory BK-opener activity. The presence of a phenolic function, with a possible H-bond donor role is confirmed. The presence of nitrogen heterocycles on the acid side of the amide linker seems to be a negative requirement, while furan and thiophene are well tolerated. The introduction of insaturated heterocyclic rings on the basic side of the amide linker, led to satisfactory biological activity, while the presence of aliphatic heterocycles lowered the pharmacological effect.

Computational simulations of HIV-1 proteases-multi-drug resistance due to nonactive site mutation L90M.

Hirotaka Ode* [Chiba Univ.], Saburo Neya, Masayuki Hata, Wataru Sugiura, and Tyuji Hoshino

J. Am. Chem. Soc. **128** (25), 7887 -7895, 2006

Computational simulations of L90M PR in complex with each of three kinds of inhibitors and one typical substrate, and the mechanism of resistance are described. The L90M mutation causes changes in interaction between the side chain atoms of the 90th residue and the main chain atoms of the 25th residue, and a slight dislocation of the 25th residue causes rotation of the side chain at the 84th residue. The rotation of the 84th residue leads to displacement of the inhibitor from the appropriate binding location, resulting in a collision with the flap or loop region. The difference in levels of resistance to the three inhibitors has been explained from energetic and structural viewpoints, which provides the suggestion for promising drugs keeping its efficacy even for the L90M mutant.

Structure-based virtual screening of chemical libraries for drug discovery.

Sutapa Ghosh, Aihua Nie, Jing An and Ziwei Huang* [The Burnham Inst. for Med. Res.]

Curr. Opi. Stru.Biol. **10**, 194-202, 2006.

Virtual screening is used to high-throughput screening to improve the speed and efficiency of the drug discovery and development process. The availability of inexpensive high-performance computing platforms in recent years has transformed this field into one that is highly diverse and rapidly evolving, where large chemical databases are successfully screened to identify hits for a wide range of targets such as Bcl-2 family proteins, G protein-coupled receptors, kinases, metalloproteins, nuclear hormone receptors, proteases and many more.

Medicinal Chemistry and Drug Design (cont'd)

Aptamer therapeutics advance.

J.F. Lee, G.M. Stovall and A.D. Ellington* [Univ. of Texas at Austin]

Curr. Opi. Stru.Biol. **10**, 282-289, 2006.

Aptamers have definite advantages over antibodies, chemically synthesized and modifications are introduced that improve their stabilities and pharmacokinetic properties. A number of aptamers against therapeutically important targets have shown efficacy in cell and animal models. Advances in selection technologies and a more thorough exploration of how to deliver nucleic acids to target cells and tissues should further speed the process of drug development.

An integrated in silico 3D model-driven discovery of a novel, potent, and selective amidosulfonamide 5-HT_{1A} agonist (PRX-00023) for the treatment of anxiety and depression.

O.M. Becker* [Predix Pharm.], D.S. Dhanoa, Y.Marantz, D.Chen, S.Shacham, C.Srinivasa, A. Heifetz, P. Mohanty, M. Fichman, A. Sharadendu, R. Nudelman, M. Kauffman, and S. Noiman

J. Med. Chem., **49** (11), 3116 -3135, 2006

PREDICT methodology is used to model the structure of 5-HT_{1A} and performing in silico screening on that structure leading to discover a lead compound. The lead compound is optimized following a strategy devised based on in silico 3D models. In vivo preclinical and Phase-I clinical data for 20m tolerability, pharmacokinetics, and pharmacodynamics studies are reported. This is the first report for a Phase-III drug candidate that is discovered and optimized, from start to finish, using in silico model-based methods as the primary tool.

A!
The discovery of new 11β-hydroxysteroid dehydrogenase type-1 inhibitors by common feature pharmacophore modeling and virtual screening.

D. Schuster, E.M. Maurer, C. Laggner, L.G. Nashev, T. Wilckens, T. Langer*[Univ. of Berne], and A. Odermatt

J. Med. Chem., **49** (11), 3454-3466, 2006.

Catalyst is used to develop ligand-based multifeature pharmacophore models for 11β-HSD1 inhibitors. The results suggested that inhibitor-based pharmacophore models for 11β-HSD1 in combination with suitable cell-based activity assays, including such for related enzymes, could be used for the identification of selective and potent inhibitors.

A!
Refining the multiple protein structure pharmacophore method: Consistency across three independent HIV-1 protease models.

K.L. Meagher, M.G. Lerner, and H.A. Carlson* [Univ. of Michigan]

J. Med. Chem., **49** (11), 3478-3484, 2006

Multiple protein structures (MPS) approach is used to create a receptor-based pharmacophore model of the desired target. This is applied to all three unbound crystal structures of HIV-1p. This is improved with denser probe mapping of the binding site and refined the selection criteria for pharmacophore elements. This improved protocol has led to the development of a consistent 8-site pharmacophore model for HIV-1p, which is independent of starting structure, and a robust MPS pharmacophore method that is more amenable to automation.

Computational prediction of oral drug absorption based on absorption rate constants in humans.

J. Linnankoski, J.M. Mäkelä, Veli-Pekka Ranta, Arto Urtti* [Orion Pharma.] and M. Yliperttula.

J. Med. Chem., **49** (11), 3674-3681, 2006

The relationships between the K_a values of the 22 structurally diverse drugs and computational molecular descriptors are established with PLS analysis. The analysis showed that the most important parameters describing log K_a are polar surface area, number of hydrogen bond donors, and log D at a physiologically relevant pH. The use of combination of only two computational molecular descriptors is possible to predict with good accuracy the K_a value for a new drug candidate.

Medicinal Chemistry and Drug Design (cont'd)

Toward understanding the structural basis of cyclin-dependent kinase 6 specific inhibition.

Heshu Lu and U. Schulze-Gahmen*[Lawrence Berkeley Nati. Lab.]

J. Med. Chem., **49** (11), 3826-3831, 2006

CDK4 and CDK6 enzymes are described with the structures of human CDK6 with a very specific kinase inhibitor, based on a pyrido[2,3-*d*]pyrimidin-7-one scaffold, and with the less specific aminopurvalanol inhibitor. The results suggested that relatively small conformational differences between CDK2 and CDK6 in the hinge region are contributing to the inhibitor specificity by inducing changes in the inhibitor orientation that lead to sterical clashes in CDK2 but not CDK6. These complex structures provided valuable insights for the future development of CDK-specific inhibitors.

Discovery, structure-activity relationship study, and oral analgesic efficacy of cyproheptadine derivatives possessing N-type calcium channel inhibitory activity.

T. Yamamoto, S. Niwa, S. Iwayama, H. Koganei, Shin-ichi Fujita, T. Takeda, M. Kito, Y. Ono, Y. Saitou, A. Takahara, S. Iwata, H. Yamamoto and M. Shoji* [Ajinomoto Company Inc.]

Bioorg. Med. Chem. **14**, 5333-5339 (2006)

Antiallergic drug cyproheptadine (Cyp) is known to have inhibitory activities for L-type calcium channels in addition to histamine and serotonin receptors. Cyp has an inhibitory activity against N-type calcium channel, is optimized to obtain more selective N-type calcium channel blocker with analgesic action. A potent N-type calcium channel inhibitory activity which had lower inhibitory activities against L-type calcium channel, histamine (H_1), and serotonin ($5\text{-}HT_{2A}$) receptors than those of Cyp-**13** showed an oral analgesic activity in rat formalin-induced pain model.

Targeting cancer cells: Magnetic nanoparticles as drug carriers.

C. Alexiou*[Univ. of Erlangen-Nurnberg], R.J. Schmid, R. Jurgons, M. Kremer, G. Wanner, C. Bergemann, E. Huenges, T. Nawroth, W. Arnold and F.G. Parak.

J. Euro.Biophys. **35**, 446-450, 2006.

Iron oxide nanoparticles are used covered by starch derivatives with phosphate groups which bound mitoxantrone as chemotherapeutikum. In the present work, a strong magnetic field gradient at the tumour location accumulates the nanoparticles is showed. Electron microscope investigations showed that the ferrofluids could be enriched in tumour tissue and tumour cells.

Structural and electronic characterization of antioxidants from marine organisms.

M. Belcastro, T. Marino, N. Russo* [Univ. of Calabria] and M. Toscano.

*Theor.Chem.Accounts.***115**, 361-369 (2006)

DFT with B3LYP/6-311++G** level is used to investigate the molecular properties of new systems that serve as antioxidants. These studies are performed in gas phase and in solvent. The results showed that the hydroquinone derivatives have the greatest potentiality as antioxidants between the studied systems.

Quantitative Structure-Activity Relations

Discovery, structure-activity relationship study, and oral analgesic efficacy of cyproheptadine derivatives possessing N-type calcium channel inhibitory activity.

Takashi Yamamoto, Seiji Niwa, Satoshi Iwayama, Hajime Koganei, Shin-ichi Fujita, Tomoko Takeda, Morikazu Kito, Yukitsugu Ono, Yuki Saitou, Akira Takahara, Seinosuke Iwata, Hiroshi Yamamoto and Masataka Shoji* [Ajinomoto company Inc.]

Bioorg. Med. Chem. **14**, 5333-5339 (2006)

Antiallergic drug cyproheptadine (Cyp) is known to have inhibitory activities for L-type calcium channels in addition to histamine and serotonin receptors. Cyp had an inhibitory activity against N-type calcium channel, is optimized to obtain more selective N-type calcium channel blocker with analgesic action. A potent N-type calcium channel inhibitory activity which had lower inhibitory activities against L-type calcium channel, histamine (H_1), and serotonin ($5\text{-}HT_{2A}$) receptors than those of Cyp-**13** showed an oral analgesic activity in rat formalin-induced pain model.

Antiproliferative effect of Baylis-Hillman adducts and a new phthalide derivative on human tumor cell lines.

Luciana K. Kohn, C.H. Pavam, D. Veronese, F. Coelho, J.E. De Carvalho and Wanda P. Almeida* [Medical Sciences Faculty/Unicamp]

Euro. J. Med. Chem. **41**, 738-744 (2006)

Qualitative structure-activity relationship studies showed that carbon-carbon double bond and the presence of an electron-withdrawing substituent at the aromatic ring are essential for the activity. A quinoline-phthalide derivative has exhibited a potent effect on the proliferation of all cell lines and their special cytotoxic activity against NCIADR cell line.

Solid-phase synthesis and pharmacological evaluation of a library of peptidomimetics as potential farnesyltransferase inhibitors: An approach to new lead compounds.

P. Gilleron, R. Millet, R. Houssin, N. Wlodarczyk, A. Farce, A. Lemoine, J.-F. Goossens, P. Chavatte, N. Pommery and J.-P. Hénichart* [Univ. de Lille-II]

Euro. J. Med. Chem. **41**, 745-755 (2006)

Inhibitors of Oncogenic Ras enzyme is developed as potential anti-cancer drugs, particularly based on the structure of the CA_1A_2X carbonyl terminus of Ras. Multipin method is used to measure the activity and their molecular docking in the active site of the enzyme provides details on key interactions with the protein.

Prediction of standard Gibbs energies of the transfer of peptide anions from aqueous solution to nitrobenzene based on support vector machine and the heuristic method.

Luan Feng, Zhang Xiaoyun, Zhang Haixia, Zhang Ruisheng* [Lanzhou Univ.], Liu Mancang, Hu Zhide and Fan Botao

J.Comp. Aided Mol.Design.**20**, 1-11 (2006)

QSPR is performed to predict the standard Gibbs energies of the transfer of peptide anions from aqueous solution to nitrobenzene. The four molecular descriptors selected by the heuristic method (HM) in Comprehensive Descriptors for Structural and Statistical Analysis (CODESSA) are used as inputs for support vector machine and radial basis function neural networks. The results obtained by the novel machine learning technique, SVM, are compared with those obtained by HM and RBFNN. The results are well agreed with the experimental values and provided a potential method for predicting the physiochemical property (ΔG^{θ}) of various small peptides.

Quantitative Structure-Activity Relationships (cont'd)

Investigation of substituent effect of 1-(3,3-diphenylpropyl)-piperidinyl phenylacetamides on CCR5 binding affinity using QSAR and virtual screening techniques.

A. Afantitis, G. Melagraki, H. Sarimveis* [Nat.Tech.Univ.], P.A. Koutentis, J. Markopoulos and O. Igglessi-Markopoulou

J.Comp. Aided Mol.Design.**20**, 83-95 (2006)

QSAR model is developed with multiple linear regression analysis is applied to a series of 51 derivatives of 1-(3,3-diphenylpropyl)-piperidinyl phenylacetamides with CCR5 binding affinity. Elimination Selection-Stepwise Regression Method (ES-SWR) is used for the selection and the effects of various structural modifications on biological activity are investigated.

New ligands with affinity for the $\alpha_4\beta_2$ subtype of nicotinic acetylcholine receptors: Synthesis, receptor binding, and 3D-QSAR modeling.

K. Audouze, E. Østergaard Nielsen, G.M. Olsen, P. Ahring, T.D. Jorgensen, D. Peters, T. Liljefors, and T. Balle* [Danish Univ. of Pharm. Sci.]

J. Med. Chem., **49** (11), 3159 -3171, 2006

GRID/GLOPE approach is used to predict 3D-QSAR model for a new series of piperazines, diazepanes, diazocanes, diazabicyclononanes, and diazabicyclodecanes. Hydrogen bonding from both hydrogens on the protonated amine and from the pyridine nitrogen to a water molecule. The combination of 3D-QSAR and homology modeling proved successful for the interpretation of structure-affinity relationships as well as the validation of the individual modeling approaches.

Comparison between 5,10,15,20-tetraaryl- and 5,15-diarylporphyrins as photosensitizers: Synthesis, photodynamic activity, and quantitative structure-activity relationship modeling.

S.Banfi* [Univ. of Insubria], E.Caruso, L. Buccafurni, R. Murano, E. Monti, M. Gariboldi, Ester Papa, and P. Gramatica.

J. Med. Chem., **49** (11), 3293-3304, 2006

QSAR regression model is developed based on theoretical holistic molecular descriptors, of a series of 34 tetrapyrrolic photosensitizers. The present study explained the structural features significantly influence the photodynamic activity of tetrapyrrolic derivatives: diaryl compounds were more active with respect to the tetraarylporphyrins, and among the diaryl derivatives, hydroxy-substituted compounds were more effective than the corresponding methoxy-substituted ones.

Discovery of a novel family of SARS-CoV protease inhibitors by virtual screening and 3D-QSAR studies.

Keng-Chang Tsai, Shih-Yuan Chen, Po-Huang Liang, I-Lin Lu, Neeraj Mahindroo, Hsing-Pang Hsieh, Yu-Sheng Chao, Lincoln Liu, Donald Liu, Wei Lien, Thy-Hou Lin* [Nati.Health Res.Inst.] and Su-Ying Wu*

J. Med. Chem., **49** (11), 3485-3495, 2006.

In this study, a compound database is screened by the structure-based virtual screening approach to identify initial hits as inhibitors of SARS-CoV $3CL^{pro}$. 59,363 compounds are docked, 93 are selected for the inhibition assay, and 21 showed inhibition against SARS-CoV $3CL^{pro}$, with three of them having common substructures. Maybridge, ChemBridge, and SPECS-SC databases led to the identification of another 25 compounds that exhibited inhibition against SARS-CoV 3CLpro. 28 compounds are subjected to 3D-QSAR studies to elucidate the pharmacophore of SARS-CoV 3CLpro.

Zeolites

Gibbs ensemble Monte Carlo simulation of supercritical CO_2 adsorption on Na*A* and Na*X* zeolites.

S. Liu and X. Yang* [Nanjing Univ. of Tech.]

J. Chem. Phys. **124**, 244719-244725 (2006)

MC simulation is used to study the adsorption of supercritical carbon dioxide on two kinds of zeolites with identical chemical composition with different pore structure Na*A* and Na*X*. The adsorption behaviors of supercritical CO_2 on the Na*A* and Na*X* zeolites, based on the adsorption isotherms and isosteric heats of adsorption, are discussed in detail and are compared with the experimental results.

Enzyme Catalysis

On the nature of oxoiron (IV) intermediate in dioxygen activation by non-heme enzymes.

A.V. Nemukhin, I.A. Topol* [Nat. Cancer Inst. at Frederick], R.E. Cachau and S.K. Burt.

Theor.Chem.Accounts: Theory, Computation, and Modeling. **115**, 348-353 (2006)

Electronic properties of the molecular systems with the short distance Fe-O unit, which are presumably formed as reaction intermediates during oxygen activation by non-heme enzymes. The non-heme enzymatic intermediates are assigned to the systems with the oxidation state of Fe between III and IV, as recently proposed for the TauD enzyme in experimental studies.

Carbon Nanoparticles

Sol-Gel assembly of CdSe nanoparticles to form porous aerogel networks.

I.U. Arachchige and Stephanie L. Brock* [Wayne State Univ.]

J. Am. Chem. Soc. **128** (25), 7964 -7971, 2006

CdSe aerogels prepared by oxidative aggregation of primary nanoparticles, followed by CO_2 supercritical drying studies are described. The resultant materials are mesoporous, with an interconnected network of colloidal nanoparticles, and exhibit BET surface areas up to 224 m^2/g and BJH average pore diameters in the range of 16-32 nm. The specific optical characteristics of the aerogel could further modified by surface ligand exchange at the wet-gel stage, without destroying the gel network.

Longitudinal polarizability of carbon nanotubes.

E.N. Brothers* [Princeton Univ.], G.E. Scuseria, and K.N. Kudin.

J. Phys. Chem. B. **110** (26), 12860-12864 (2006)

DFT is used to determine the longitudinal polarizabilities of carbon nanotubes. The polarizability per atom of a nanotube in the axial direction is primarily determined by the band gap. This is explained in terms of the sum over states equation used to determine polarizability and noting that the vast majority of the polarizability arises from a few elements near the band gap. This universal trend is then used with experimentally determined band gaps to predict the experimental polarizability of carbon nanotubes.

Ozonization at the vacancy defect site of the single-walled carbon nanotube.

L. Vincent Liu, W. Quan Tian, and Y. Alexander Wang* [Univ. of British Columbia]

J. Phys. Chem. B. **110** (26), 13037-13044 (2006)

Ab initio based MD simulations within a two layered ONIOM approach is used to study the ozonization at the vacancy defect site of the single-walled carbon nanotube. The reaction involving the unsaturated active carbon atom is the most probable pathway, where ozone undergoes fast dissociation at the active carbon atom at 300 K. The results provide a microscopic understanding of the ozonization at the vacancy defect site of the single-walled carbon nanotube.

1.2. *Biopolymers*

Bioinformatics

Transition networks for the comprehensive characterization of complex conformational change in proteins.

Frank Noé, D. Krachtus, J.C. Smith, and S. Fischer* [Univ. of Heidelberg]

J.Chem. Theor. and Comp. **2**, 840-857 (2006)

The computation of a TN is achieved for a complex protein transition is presented. An efficient hierarchical procedure is used to uniformly sample the conformational subspace relevant to the transition. The best path which connects the end states is determined as well as the rate-limiting ridge on the energy surface which separates them. Graph-theoretical algorithms permit this to be achived by computing the barriers of only a small number out of the many subtransitions in the TN.

Genetic algorithms as a tool for helix design – computational and experimental studies on prion protein helix 1.

J. Ziegler* [Univ. of Bayreuth] and S. Schwarzinger

J.Comp. Aided Mol.Design.**20**, 47-54 (2006)

AGADIR energy function, an evolutionary approach to optimize helix stability in peptides and proteins employing for helix stability as scoring function. This algorithm is capable of developing stable helical scaffolds containing a wide variety of structural and functional amino acid patterns. This is applied for the optimization of the stability of prion protein helix 1, plays an important role in the conformational transition from the cellular to the pathogenic form of the prion protein. This is an interesting target for pharmacological as well as genetic engineering approaches to counter the uncurable prion diseases.

Protein Secondary Structure

2D representation of protein secondary structure sequences and its applications.

Liwei Liu*[Dalian Univ. of Tech.], Tianming Wang

J.Comp. Chem. **27,** 1119-1124 (2006)

2D representation of protein secondary structure sequences is proposed to display, analyze, and compare the secondary structure sequences. Based on this representation, the structural class to the protein, and verify the advantage or disadvantage of the methods of predicted protein second structure.

Protein Structure Prediction

Crystallographic studies on *N*-azidoacetyl-β-D-glucopyranosylamine, an inhibitor of glycogen phosphorylase: Comparison with *N*-acetyl-β-D-glucopyranosylamine.

E.I. Petsalakis, E.D. Chrysina, C. Tiraidis, T.Hadjiloi, D.D. Leonidas, N.G. Oikonomakos* [Inst. of Org. and Pharm.Chem.], Udayanath Aich, B.Varghese and D. Loganathan.

Bioorg. Med. Chem. **14**, 5316-5324 (2006)

The ligand structure in complex with GPb at 2.03 A^o resolution is determined. Azido-NAG is accommodated in the catalytic site of T-state GPb at the same position as that of NAG and stabilizes the T-state conformation of the 280s loop by making several favorable contacts to residues of this loop. The difference observed in the K_i values of the two analogues is interpreted in terms of desolvation effects, subtle structural changes of protein residues and changes in water structure.

Protein Structure Prediction (cont'd)

Protein structure prediction: The next generation.

M.C. Prentiss, Corey Hardin, M.P. Eastwood, Chenghang Zong, and P.G. Wolynes* [Univ. of Illinois]

J.Chem. Theor. and Comp. **2**, 705-716 (2006)

Protein folding kinetics based on energy landscape ideas are useful to predict the protein structure and for the development of coarse grained models. The second generation prediction energy functions are developed by introducing information from an ensemble of previously simulated structures. First generation simulated structures provide an improved input for associative memory energy functions in comparison to the experimental protein structures chosen on the basis of sequence alignment.

Structural basis of the inhibition of Golgi α-Mannosidase II by mannostatin A and the role of the thiomethyl moiety in ligand-protein interactions.

S.P. Kawatkar, D.A. Kuntz, R.J. Woods, D.R. Rose, and Geert-Jan Boons* [Univ. of Toronto]

J. Am. Chem. Soc. **128** (25), 8310 -8319, 2006

The structures of mannose trimming enzyme *drosophila* Golgi α-mannosidase II (dGMII) complexed with the inhibitors mannostatin A and an *N*-benzyl analogue is determined. Possible conformations of the mannosyl oxacarbenium ion and an enzyme-linked intermediate are compared to the conformation of mannostatin A in the cocrystal structure with dGMII. It is found that mannostatin A best mimics the covalent linked mannosyl intermediate, which adopts a $^{1}S_{5}$ skew boat conformation.

Quantum mechanical and molecular dynamics simulations of ureases and Zn β-lactamases.

G. Estiu, D. Suárez, K.M. Merz, Jr* [Univ. of Florida]

J.Comp. Chem. **27,** 1240-1262 (2006)

The use of different methodologies, including quantum chemical calculations, MD simulations, as well as mixed QM/MM approaches to understand the structure and function of metallo-β-lactamases and ureases are described.

Transition metal catalyzed methods for site-selective protein modification.

J.M. Antos and M.B. Francis* [Lawrence Berkeley Nationals Labs.]

Curr. Opi. Stru.Biol. **10**, 253-262, 2006.

Chemical reactions that target alternative amino acid side chains or unnatural functional groups are emerging as a valuable complement to more commonly used lysine- and cysteine-based strategies. Transition metal catalysis to protein modification resulted in new methods for protein cross-linking, tryptophan modification, tyrosine modification, reductive amination of protein amines, and unnatural amino acid labeling. These strategies expanded the synthetic flexibility of protein modification, and thus the range of applications for which bioconjugates could be used in chemical biology and materials science.

Hydrophobic and acidic moments of a nucleoplasmin NP-core chaperone.

B. David Silverman* [IBM Thomas J. Watson Res. Cent.]

J. of Biomol. Stru. and Dyn. 24(1), 49-56, 2006.

The present studies provide a measure of the hydrophobic residue burial about the different interfaces and centers of the NO38-core multimeric structure. The hydrophobic "pentameric ring," comprised of the hydrophobic cores of the monomers and prevalence of non-polar residues at their interfaces is observed. A hydrophobic bias with respect to the center of the pentamer is found, and expected to contribute to the thermostability of the multimer. Structural and chromatographic analysis showed the NO38-core chaperone to bind $(H3\text{-}H4)_2$ histone tetramers as well as H2A-H2B dimers.

Crystal structure prediction using *ab initio* evolutionary techniques: Principles and applications. A.R. Oganov and C.W. Glass* [ETH Zurich] *J. Chem. Phys*. **124**, 244704-244718 (2006)	An evolutionary algorithm with *ab* initio calculations is developed to predict the crystal structure. This method allows one to predict the most stable crystal structure and a number of low-energy metastable structures for a given compound at any *P-T* conditions without requiring any experimental input.

Comparative or Homology Modeling

Comparison of a homology model and the crystallographic structure of human 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1) in a structure-based identification of inhibitors. L. Miguet, Z. Zhang, M. Barbier and M.G. Grigorov* [China Agri. Univ.] *J.Comp. Aided Mol.Design*.**20**, 67-81 (2006)	An *in silico* screening study to identify new selective inhibitors of human 11βHSD1 enzyme. Homology modeling is used to construct the 3D structure of 11βHSD. Molecular docking is used to validate the predicted model by showing that it is able to discriminate between known 11βHSD1 inhibitors or substrates and non-inhibitors. The homology model is found to reproduce closely the crystal structure. Structure-based virtual screening experiments carried out on both the homology model and the crystallographic structure with a database of 114'000 natural molecules. 15 molecules were consistently selected as inhibitors based on both the model and crystal structures of the enzyme from the above studies.
Construction of human ghrelin receptor (hGHS-R1a) model using a fragmental prediction approach and validation through docking analysis. A. Pedretti, M. Villa, M. Pallavicini, E. Valoti, and G. Vistoli* [Univ. di Milano] *J. Med. Chem.,* **49** (11), 3077 -3085, 2006	The reliability of a fragmental approach to build a full-length model of the human ghrelin receptor (hGHS-R1a) in its open state is investigated. Docking analysis confirmed the relevance of two distinct subpockets: a polar cavity bearing the key residues involved in receptor activation and an aromatic/apolar subpocket, plays a key role in determining the high constitutive activity of hGHS-R1a.
Homology modeling of human serum carnosinase, a potential medicinal target, and MD simulations of its allosteric activation by citrate. Giulio Vistoli* [Univ. of Milano], Alessandro Pedretti, Matteo Cattaneo, Giancarlo Aldini, and Bernard Testa *J. Med. Chem.,* **49** (11), 3269 -3277, 2006	Serum carnosinase, its catalytic site modeling and to unravel the molecular mechanism by which citrate ions increase the catalytic efficiency of serum carnosinase is presented. A homology model of the enzyme is obtained on the basis of β-alanine synthetase, and its active center is found to bind known substrates carnosine, homocarnosine, and anserine in a binding mode conducive to catalysis. MD simulations evidenced that citrate binding has a remarkable conformational influence on the 3D structure of carnosinase, increasing the binding affinity of carnosine to the catalytic site.

Protein Folding

A study of density of states and ground states in hydrophobic-hydrophilic protein folding models by equi-energy sampling.

S. C. Kou, Jason Oh and W. Hung Wong* [Stanford Univ.]

J. Chem. Phys. **124**, 244903-244912 (2006)

An equi-energy (EE) sampling approach is used to study protein folding in the two-dimensional hydrophobic-hydrophilic (HP) lattice model. This approach enables efficient exploration of the global energy landscape and provides accurate estimates of the density of states, which allowed to conduct a detailed study of the thermodynamics of HP protein folding.

Low-dimensional, free-energy landscapes of protein-folding reactions by nonlinear dimensionality reduction.

P. Das, M. Moll, H. Stamati, L.E. Kavraki, and C. Clementi* [Baylor College of Med.]

PNAS.103, 9885-9890 (2006)

A general approach is proposed and validated by characterizing the folding landscape associated with a coarse-grained protein model of src homology 3 as sampled by MD simulations. The dimensionality reduction is correctly identified the transition-state ensemble of the reaction. The first embedding dimension efficiently captures the evolution of the folding process along the main folding route. The proposed method is efficiently find a low-dimensional representation of a complex process such as protein folding.

Protein Design and Engineering

Enzymatic tools for engineering natural product glycosylation.

S. Blanchard and J.S. Thorson* [Univ. of Wisconsin-Madison]

Curr. Opi. Stru.Biol. **10**, 263-271, 2006.

'Combinatorial biosynthesis', is an emerging method that relies upon the co-expression of sugar biosynthetic gene cassettes and glycosyltransferases in a host organism to generate novel glycosylated natural products. A recent progress in combinatorial biosynthesis is highlighted in this review, emphasizing the elucidation of nucleotide-sugar biosynthetic pathways and recent developments on glycosyltransferases.

Protein Hydration

Hybrid quantum/classical molecular dynamics for a proton transfer reaction coupled to a dissipative bath.

S. Young Kim and S. Hammes-Schiffer* [Pennsylvania State Univ.]

J. Chem. Phys. **124**, 244102-244113 (2006)

A hybrid quantum/classical molecular dynamics approach is applied to a proton transfer reaction represented by a symmetric double well system coupled to a dissipative bath. In this approach, the proton is treated quantum mechanically and all bath modes are treated classically. The results are well agreed with the spatial-diffusion-controlled regime. The results have important implications for future applications to hydrogen transfer reactions in solution and proteins.

Observation of fragile-to-strong dynamic crossover in protein hydration water.

S.-H. Chen*[Massachusettes Inst. of Tech.],L. Liu, E. Fratini, P. Baglioni, A. Faraone, and E. Mamontov

PNAS.**103**, 9012-9016 (2006)

The hydrated protein is able to sample more conformational states and biologically functional at 220 K temperature. This sudden dynamic behavior of the hydration water on lysozyme occurs precisely at 220 K and is described as a fragile-to-strong dynamic crossover. At the fragile-to-strong dynamic crossover, the structure of hydration water makes a transition from predominantly high-density (more fluid state) to low-density (less fluid state) forms derived from the existence of the second critical point at an elevated pressure.

Protein Dynamics

Collective dynamics of EcoRI-DNA complex by elastic network model and molecular dynamics simulations.

Pemra Doruker* [Bogazici Univ.], Lennart Nilsson, Ozge Kurkcuoglu

J. of Biomol. Stru. and Dyn. **24(1)**, 1-16, 2006.

Anisotropic network model (ANM) is used to analyze the collective motions of restriction enzyme EcoRI in free form and in complex with DNA. MD simulations are performed for the EcoRI-DNA complex in explicit water. The residues that make specific and non-specific interactions with the DNA exhibit very low fluctuations in the free enzyme. Dynamic domains in EcoRI complex and cross-correlations between residue fluctuations indicate possible means of communication between the distal active sites.

Membrane Proteins and Lipid-Peptide Interactions

Assignment of the first photoelectron band of $CH_3CHBr(X^2A)$ using ab-initio and density functional theory (DFT) computational calculations.

M. H. N. Zamanpour*[Univ. of California] and G. Ebrahimzadeh.

J.Chem. Theor.and Comp. **2**, 472-483 (2006)

Simulation algorithms for the dynamics of elastic membrane sheets embedded in a fluid medium are extended to inhomogeneous hydrodynamic environments. The hydrodynamic environment of the membrane leads to significant changes in dynamics, and the effects are discussed.

Multiscale coarse-graining of mixed phospholipid /cholesterol bilayers.

Sergei Izvekov and Gregory A. Voth* [Univ. of Utah]

J.Chem. Theor. and Comp. **2**, 637-648 (2006)

Multiscale coarse-graining method is used to construct coarse-grained models for mixed dimyristoyl-phosphatidylcholine/cholesterol lipid bilayers. The CG sites for lipid and cholesterol molecules are associated with the centers-of-mass of atomic groups. A one-site MS-CG model based on the TIP3P potential was used for water, with the interaction site placed at the molecular geometrical center, and the analytical fit of the model is presented.

Interaction between K^+ channel gate modifier hanatoxin and lipid bilayer membranes analyzed by molecular dynamics simulation.

M. Nishizawa and K. Nishizawa* [Teikyo Univ.]

J. Euro.Biophys. **35**, 373-381, 2006

MD simulations are carried out for HaTx1, a variant of HaTx, in fully hydrated phospholipid bilayers. The system reproduced the surface-binding mode of HaTx1, in which HaTx1 resided in the extracellular side of the water/membrane interface with the hydrophobic patch of HaTx1 facing the membrane interior. Various parameter settings suggested that the surface-binding mode is unstable because of the substantial attractive electrostatic force between HaTx1 and the lipid head groups of the inner leaflet.

Membrane Proteins and Lipid-Peptide Interactions

Actin and amphiphilic polymers influence on channel formation by syringomycin E in lipid bilayers.

A.N. Bessonov, L.V. Schagina, J.Y. Takemoto, P.A. Gurnev, I.M. Kuznetsova, K.K. Turoverov and V.V. Malev* [St. Petersburg State Univ.]

J. Euro.Biophys. **35**, 382-392, 2006

The G-actin increased the SRE-induced membrane conductance due to formation of additional SRE-channels. Actin binds to the lipid bilayer and binding is a limiting step for SRE-channel formation. The increase in the SRE membrane activity is due to hydrophobic interactions between the adsorbing molecules and membrane. Hydrophobic interactions are not sufficient for the increase of SRE channel-forming activity. The dependence of the number of SRE-channels on the concentration of adsorbing species gave an *S*-shaped curve indicating cooperative adsorption of the species.

Bilayer lipid composition modulates the activity of dermaseptins, polycationic antimicrobial peptides.

Hervé Duclohier*[UNRS-Univ. de Poitiers]

J. Euro.Biophys. **35**, 401-409, 2006

The ion specificity of its pores induced in bilayers is modulated by phospholipid-charged headgroups. This suggests mixed lipid–peptide pore lining instead of the more classical barrel–stave model. Concentration dependence suggests that the pores are mainly formed by dermaseptin tetramers. The two most probable single-channel events are well resolved at 200 and 500 pS with occasional other equally spaced higher or lower levels.

Lipid model membranes for drug interaction study.

L. P. Cavalcanti* [European Synch. Radiation Facility], O. Konovalov and I. L. Torriani.

J. Euro.Biophys. **35**, 431-438, 2006

The structural study on the process of incorporation of a hydrophobic drug, Ellipticine (ELPT), into lipid model membranes for drug targeting purpose. The ELPT is an alkaloid that showed an anti-proliferation activity against several types of tumor cells and against the HIV1 virus. The zwitterionic lipid dipalmitoyl phosphatidylcholine (DPPC) and four different anionic lipids: cardiolipin (CL), dipalmitoyl phosphatidic acid (DPPA), dipalmitoyl phosphatidylglycerol (DPPG) and dipalmitoyl phosphatidylserine (DPPS), both spread on a Langmuir monolayer and deposited on a solid substrate are used to mimic a model membrane and study the interaction with the drug ELPT.

Spatial modeling of dimerization reaction dynamics in the plasma membrane: Monte Carlo vs. continuum differential equations.

Kapil Mayawala* [Univ. of Delware], D.G. Vlachos and J.S. Edwards

J.Biophys. 122, 194-208, 2006.

MD simulations showed that the effective reaction rate constant decreases with time due to time dependent changes in the spatial distribution of receptors. The effective reaction rate constant of simple PDEs differ from that of MC by up to two orders of magnitude. The fluctuations in the number of copies of signaling proteins depending on the diffusion properties of the system. The results showed that localization of epidermal growth factor receptor (EGFR) could cause the diffusion limited dimerization rate to be up to two orders of magnitude higher at higher average receptor densities reported for cancer cells, as compared to a normal cell.

Membrane Proteins and Lipid-Peptide Interactions

Membrane protein dynamics and detergent interactions within a crystal: A simulation study of OmpA.

P.J. Bond, J.D. Faraldo-Gómez* [Univ. of Oxford], S.S. Deol, and M.S.P. Sansom

PNAS.**103**, 9518-9523 (2006)

MD simulations are used to explore the dynamics of outer membrane protein OmpA in its crystal environment. The previously undescribed structure and dynamics of detergent molecules in a unit cell providing insight into the interactions important in the formation and stabilization of the crystalline environment at room temperature. It was observed that at room temperature the detergent molecules form a dynamic, extended micellar structure spreading over adjacent OmpA monomers within the crystal.

Ligand Binding

A new structural theme in C_2-symmetric HIV-1 protease inhibitors: O*rtho*-substituted P1/P1′ side chains.

Johan Wannberg, Yogesh A. Sabnis, Lotta Vrang, Bertil Samuelsson, Anders Karlén, Anders Hallberg and Mats Larhed* [Uppsala Univ.]

Bioorg. Med. Chem. **14**, 5303-5315 (2006)

Computational techniques are applied to study the binding mode of inhibitors and to establish structure-activity relationships. The overall orientation of the inhibitors in the active site is reproduced by docking. The results suggested three possible conformations of the P1/P1′ groups, two are of more plausible.

Aptamers selected for higher-affinity binding are not more specific for the target ligand.

J.M. Carothers, S.C. Oestreich, and J.W. Szostak* [Simches Res. Cent.]

J. Am. Chem. Soc. **128** (25), 7929 -7937, 2006.

The binding specificities of the eleven GTP aptamers by carrying out competition binding studies with sixteen different chemical analogues of GTP are examined. The aptamers have distinct patterns of specificity, implying that each RNA is a structurally unique solution to the problem of GTP binding. The results suggested that the simplest way to improve aptamer K_ds will increase the stability of the RNA tertiary structure with additional intramolecular RNA-RNA interactions.

Novel bis(1*H*-indol-2-yl)methanones as potent inhibitors of FLT3 and platelet-derived growth factor receptor tyrosine kinase.

S. Mahboobi* [Univ. of Regensburg], A. Uecker, A. Sellmer, C. Cénac, H. Höcher, H. Pongratz, E. Eichhorn, H. Hufsky, A. Trümpler, M. Sicker, F. Heidel, T. Fischer, C. Stocking, S. Elz, Frank-D. Böhmer, and S. Dove

J. Med. Chem., **49** (11), 3101 -3115, 2006.

Bis(1*H*-indol-2-yl)methanones are found to inhibit FLT3 and PDGFR kinases and to optimize FLT3 activity and selectivity, 35 novel derivatives are tested for inhibition of FLT3 and PDGFR autophosphorylation. Docking at the recent FLT3 structure suggested a bidentate binding mode with the backbone of Cys-694. Activity and selectivity is related to interactions of one indole moiety with a hydrophobic pocket including Phe-691, the only different binding site residue (PDGFR Thr-681).

A combination of docking/dynamics simulations and pharmacophoric modeling to discover new dual c-Src/Abl kinase inhibitors.

Fabrizio Manetti, G.A. Locatelli, Giovanni Maga, Silvia Schenone, Michele Modugno, Stefano Forli, Federico Corelli, and Maurizio Botta* [Inst. of Gen. Molecolare]

J. Med. Chem., **49** (11), 3278-3286, 2006

Docking and dynamics calculations are used to build three-dimensional models of the complexes between Src and several of its known inhibitors. Activities of the inhibitors due to the interactions contribution are codified into pharmacophoric models, which in turn applied to perform a search of available compounds within the Asinex database. 1,3,4-thiadiazoles and pyrazolydine-3,5-diones shows inhibitory activity in the submicromolar range in a cell-free assay toward Src.

Ligand Binding

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MolDock: A new technique for high-accuracy molecular docking.

René Thomsen* [Molegro ApS] and M.H. Christensen

J. Med. Chem., **49** (11), 3315-3321, 2006.

MolDock is based on a new heuristic search algorithm that combines differential evolution with a cavity prediction algorithm. The docking scoring function of MolDock is an extension of the piecewise linear potential including new hydrogen bonding and electrostatic terms. The docking accuracy of MolDock is evaluated by docking flexible ligands to 77 protein targets and is able to identify the correct binding mode of 87% of the complexes. The accuracy of Glide and Surflex is 82% and 75%, and FlexX obtained 58% and GOLD 78% on subsets containing 76 and 55 cases respectively.

Binding mode prediction of strand transfer HIV-1 integrase inhibitors using Tn5 transposase as a plausible surrogate model for HIV-1 integrase.

M. Letizia Barreca* [Univ. of Messina], L. De Luca, N. Iraci, and A. Chimirri.

J. Med. Chem., **49** (11), 3994-3997, 2006

The crystal structure of Tn5 transposase-DNA complex is used in docking studies to predict binding modes of HIV-1 integrase strand transfer inhibitors (INSTIs). The identification of HIV-1 integrase inhibitors from an in vitro screen using Tn5 transposase as the target has been recently reported. The results suggested that the utility of this protein is useful to surrogate model for IN and also for in silico screening, in the search for new potential INSTIs.

Protein-Protein Interactions

An analytical electrostatic model for salt screened interactions between multiple proteins.

Itay Lotan and T. Head-Gordon* [Univ. of California]

J.Chem. Theor.and Comp. **2**, 541-555 (2006)

A new general analytical solution for computing the screened electrostatic interaction between multiple macromolecules of arbitrarily complex charge distributions, assumed that they are described by spherical low dielectric cavities in a higher dielectric medium. While the current formulation describes solutions based on simple spherical geometries, it appears possible to reformulate these electrostatic expressions to smoothly increase spatial resolution back to greater molecular detail of the dielectric boundaries.

Carbonic anhydrase inhibitors: X-ray and molecular modeling study for the interaction of a fluorescent antitumor sulfonamide with isozyme II and IX.

V. Alterio, R. Maria Vitale, S. Maria Monti, C. Pedone, A. Scozzafava, A. Cecchi, G. De Simone, and C.T. Supuran* [Univ. degli Stu. di Firenze]

J. Am. Chem. Soc. **128** (25), 8329 -8335, 2006

The crystal structure of the carbonic anhydrase inhibitor (4-sulfamoylphenylethyl)thioureido fluorescein in complex with the cytosolic isoform hCA II is reported. Its binding to hCA II is similar to that of other benzesulfonamides, with the ionized sulfonamide coordinated to the Zn^{2+} ion within the enzyme active site, and also participating in a network of hydrogen bonds with residues Thr-199 and Glu-106. The bulky tricyclic fluorescein moiety is located at the rim of the active site, on the protein surface, and strongly interacted with the α-helix formed by residues Asp130-Val135.

Protein-Protein Interactions (cont'd)

Development of small molecules designed to modulate protein-protein interactions

Ye Che* [Nat. Inst. of Health], B.R. Brooks and Garland R. Marshall

J.Comp. Aided Mol.Design.**20**, 109-130 (2006)

A general approach based on the "privileged-structure hypothesis" is described. Any organic templates capable of mimicking surfaces of protein-recognition motifs are potential privileged scaffolds as protein-complex antagonists-to address the challenges inherent in the discovery of small-molecule inhibitors of protein-protein interactions.

Long-range cooperative binding effects in a T cell receptor variable domain.

Beenu Moza* [Boston Biomed. Res. Inst.], R.A. Buonpane, Penny Zhu, C.A. Herfst, A.K.M. Nur-ur Rahman, J.K. McCormick, D.M. Kranz, and E.J. Sundberg.

PNAS.**103**, 9867-9872 (2006)

Using combinatorial mutagenesis and surface plasmon resonance binding analysis to dissect additivity and cooperativity in a complex formed between a variable domain of a T cell receptor and a bacterial superantigen, the combinations of mutations from each of two hot regions exhibited significant cooperative energetics. It is proposed that these cooperative effects are propagated through a dynamic structural network. Cooperativity between hot regions has significant implications for the prediction and inhibition of protein-protein interactions.

Nucleic Acids

Coronavirus phylogeny based on 2D graphical representation of DNA sequence.

Bo Liao* [Hunan Univ.], Xuyu Xiang, Wen Zhu

J.Comp. Chem. **27,** 1196-1202 (2006)

A new approach is proposed based on the 2D graphical representation of the whole genome sequence to analyze the phylogenetic relationships of coronaviruses. The evolutionary distances are obtained through measuring the differences among the two-dimensional curves.

Possible inhibition of group-I intron RNA by resveratrol and genistein.

S. Usha, I. M. Johnson, and R. Malathi* [Univ. of Tennessee]

J. of Biomol. Stru. and Dyn. 24(1), 25-32, 2006.

In vitro studies showed that the folded structure of group I intron RNA could be a potential target site for therapeutic agents. Its presence in human pathogen like Candida albicans and absence in humans, suggested that the intron could act as an alternative therapeutic target. The binding affinity of dietary compounds resveratrol and genistein suggested that these natural compounds are binding with intron RNA and acts as an potential target and modulates the cellular process during therapeutic intervention.

Sequence structure of human nucleosome DNA.

S.B. Kogan, M. Kato, R. Kiyama and E.N. Trifonov* [Nat. Inst. of Adv. Indust. Sci. & Tech.]

J. of Biomol. Stru. and Dyn. 24(1), 25-32, 2006.

The GG and CC dinucleotides and their positions are shifted about a half-period from one another, is observed earlier for AA and TT dinucleotides. The dominance of oscillating GG and CC dinucleotides in human nucleosomes and the contribution of AG(CT), GA(TC), and AA(TT) suggested a general nucleosome DNA sequence pattern counterphase oscillation of RR and YY dinucleotides. AA and TT dinucleotides, commonly accepted as major players, are only weak contributors in the case of human nucleosomes.

Nucleic Acids (cont'd)

Prediction of RNA secondary structure by free energy minimization.

D.H. Mathews and D.H. Turner* [Univ. of Rochester]

Curr.Opi.Stru.Biol.**16**, 270-278, 2006.

The estimation of folding free energy change, the mapping of secondary structure and the implementation of computer programs for structure prediction are made. The recent trends in computer program development are: efficient use of experimental mapping of structures to constrain structure prediction; use of statistical mechanics to improve the fidelity of structure prediction; inclusion of pseudoknots in secondary structure prediction; and use of two or more homologous sequences to find a common structure.

RNA splicing: group I intron crystal structures reveal the basis of splice site selection and metal ion catalysis.

M.R. Stahley and S.A. Strobel* [Yale Univ.]

Curr.Opi.Stru.Biol.**16**, 319-326, 2006.

Azoarcus, Tetrahymena and bacteriophage Twort group I introns structures mimic different states of the splicing or ribozyme reaction pathway and provide information on splice site selection and metal ion catalysis. The 5′-splice site is selected by formation of a conserved G·U wobble pair between the 5′-exon terminus and the intron. The 3′-splice site is identified through stacking of three base triples, in which the middle triple contains the conserved terminal nucleotide of the intron, ΩG. The structures support a two-metal-ion mechanism for group I intron splicing that might have corollaries to group II intron and pre-mRNA splicing by the spliceosome.

Modeling the Lac repressor-operator assembly: The influence of DNA looping on Lac repressor conformation.

D. Swigon* [The State Univ. of NJ], B.D. Coleman, and W.K. Olson

PNAS.**103**, 9879-9884 (2006)

The theory is used to calculate the configuration and free energy of the DNA loop as a function of its length and base-pair sequence, its linking number, and the end conditions imposed by the LacR tetramer. The tetramer assumed two types of conformations. Computed loop configurations are compared with the experimental observations of permanganate sensitivities, DNase I cutting patterns, and loop stabilities. It is observed that linear DNA segments of short-to-medium chain length give rise to loops with the extended form of LacR and that loops formed within negatively supercoiled plasmids induce the V-shaped structure.

DNA detection method based on the two-dimensional aggregation and selective desorption of nanoparticle probes.

A. Charrier*[Univ. of Mediterranee] N. Candoni, and F. Thibaudau

J. Phys. Chem. B. **110** (26), 12896-12900 (2006)

A new detection method is developed based on the selective desorption of nonaggregated nanoparticles. The results are highly specific and allow the quantification of the DNA targets.

1.3. Surfaces, Catalysts, and Material Subjects

Small carbon clusters doped with vanadium metal: A density functional study of VC_n (n = 1-8).

P. Redondo* [Univ. of Valladolid], C. Barrientos, and Antonio Largo.

J.Chem. Theor. and Comp. **2**, 885-893 (2006)

DFT is used to study the different isomers of neutral VCn (n=1-8) clusters. B3LYP method with different basis sets is used to predict electronic energies, rotational constants, dipole moments, and vibrational frequencies. The electronic ground state is found to be a quartet state for even n values, whereas the ground state is a doublet for VC_3 and VC_5 and a quartet for VC_7 for odd n values.

Confined crystallization of cylindrical diblock copolymers studied by dynamic monte carlo simulations.

M. Wang, W. Hu and Yu Ma and Yu-Qiang Ma* [Nanjing Univ.]

J. Chem. Phys. **124**, 244901-244905 (2006)

MC simulations are applied for polymer crystallization and found that during the isothermal crystallization at high temperatures, crystal orientations are dominantly perpendicular to the cylinder axis at the early stage of crystal nucleation and remain to the final state.

Theoretical study of sticking processes on molecular models of silica surfaces.

G. Berthier* [Univ. of Pierre at Marie Curie], R. Savinelli, C. Adamo and I. Ciofini

Theor.Chem.Accounts: Theory, Computation, and Modeling. **115**, 379-384 (2006).

MP2 and MP4 are used to model the adsorption of small charged and neutral molecules on silica. The simplest spherosiloxane compound ($H_4Si_4O_6$) is used to mimic the surface while several molecules are considered as adsorbed species. The results identified that a strong ion-multipole interaction for the first ones and a weak dispersion-type interaction for the latter. The spherosiloxane cluster is screened by a mantle of accreted dust, the value of the binding energies, computed using the continuum dielectric theory, which is predicted to be significantly reduced.

Structure and stability of isomers of the promising interstellar molecule PC_3O.

Yang Liu, Xu-Ri Huang*[Jilin Univ.], Guang-Tao Yu, Hui-Ling Liu and Chia-Chung Sun

Theor.Chem.Accounts: Theory, Computation, and Modeling. **115**, 410-426 (2006)

DFT/B3LYP/6-311G(d) and CCSD(T)/6-311G(2d) single-point calculations are carried out for exploring the doublet potential energy surface (PES) of PC_3O, a molecule of potential interest in interstellar chemistry. The structures of the most relevant isomers and transition states are further optimized at the QCISD level followed by CCSD(T) single-point energy calculations. At the CCSD(T)/6-311G(2df)//QCISD/6-311G(d)+ZPVE level, the global minimum.

Two-Stage melting of Au-Pd nanoparticles.

S.J. Mejía-Rosales, C. Fernández-Navarro, E. Pérez-Tijerina, J.M. Montejano-Carrizales and M. José-Yacaman* [The Univ. of Texas at Austin]

J. Phys. Chem. B. **110** (26), 12884-12889 (2006)

MD simulations are performed to study the melting transition of bimetallic cuboctahedral nanoparticles of gold-palladium at different relative concentrations to study their structural properties before, in, and after the transition. It is found that the melting transition, the outer layer of the nanoparticle gets disordered, where Au atoms near the surface migrate to the surface and remain there after the particle melts as a whole.

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2. METHODOLOGY

Conformational Search and Analysis

TRAJELIX: A computational tool for the geometric characterization of protein helices during molecular dynamics simulations.

Mihaly Mezei* [New York Univ.] and Marta Filizola.

J.Comp. Aided Mol.Design.**20**, 97-107 (2006)

A new program is developed for the geometric characterization of distorted conformations of α-helices proteins. TRAJELIX, a new module within the SIMULAID framework is capable of monitoring distortions of alpha-helices in terms of their displacement, global and local tilting, rotation around their axes, compression/extension, winding/unwinding, and bending. Accurate evaluation of these global and local structural properties of the helix is helped to study the possible intramolecular and intermolecular changes in the helix packing of alpha-helical membrane proteins.

Conformational analysis of 2,2′-bifuran: Correlated high-level ab initio and DFT results.

J. C. Sancho-García and A. Karpfen* [Univ. of Alicante]

Theor.Chem.Accounts. **115**, 427-433 (2006)

Ab initio and DFT calculations are performed to study the torsional potential for inter-ring rotation. The presence of a shallow gauche minimum in the torsional potential curve. The results are used in further investigation on structure and conformational distribution of this system.

Potentials and Parameters

Replica exchange and multicanonical algorithms with the coarse-grained united-residue (UNRES) force field.

M. Nanias, C. Czaplewski, and H.A. Scheraga* [Univ. of Gdansk]

J.Chem. Theor.and Comp. **2**, 513-528 (2006)

Replica exchange method (REM), replica exchange multicanonical method (REMUCA), and replica exchange multicanonical method with replica exchange (REMUCAREM) algorithms are applied to one peptide and two small proteins to calculate the free-energy maps. The free-energy calculations showed correct folding behavior for poly-L-alanine and protein A, while for 1E0G, the native structure had the lowest free energy only at very low temperatures. The entropy contribution for 1E0G is larger than that for protein A at the same temperature.

Force-field parametrization of retro-inverso modified residues: Development of torsional and electrostatic parameters.

David Curcó, F. Rodríguez-Ropero and Carlos Alemán* [Univ. Politécnica de Catalunya]

J.Comp. Aided Mol.Design.**20**, 13-25 (2006)

QM calculations are used to develop the torsional and the electrostatic parameters for molecular mechanics studies of retro-inverso modified peptides. The resulting parameters are compared with those calculated for conventional peptides. The reliability of electrostatic models based on geometry-dependent charges and fixed charges are examined.

Potentials and Parameters (cont'd.)

Gradients of the exchange repulsion energy in the general effective fragment potential method.

Hui Li and M.S. Gordon* [Iowa State Univ.]

Theor.Chem.Accounts. **115**, 385-390 (2006)

Effective fragment potential (EFP2) method is derived and implemented for calculating the analytic gradients of the exchange-repulsion energy. The direct differentiation approach is not approximate, the gradients is used with confidence in molecular dynamics and MC simulations with the EFP2 method.

Molecular Dynamics

YUP: A molecular simulation program for coarse-grained and multiscaled models.

Robert K. Z. Tan, Anton S. Petrov, and Stephen C. Harvey* [Georgia Inst. of Tech.]

J.Chem. Theor.and Comp. **2**, 529-540 (2006)

YUP, a general-purpose program for coarse-grained and multiscaled models is developed. The MD algorithm is extended for a coarse-grained DNA model and is invisible to a standard implementation. A third model type took advantage of access to the force field to simulate the packing of DNA in viral capsids. We find that objects are easy to modify, extend, and redeploy.

Adsorption and dynamics of a single polyelectrolyte chain near a planar charged surface: Molecular dynamics simulations with explicit solvent.

Govardhan Reddy, Rakwoo Chang, and Arun Yethiraj* [Kwangwoon Univ.]

J.Chem. Theor. and Comp. **2**, 630-636 (2006)

MD simulation with explicit solvent is used to study the effect of solvent quality on the behavior of a polyelectrolyte chain near a charged surface. The polyion adsorbs completely on the surface for a high enough surface charge density, and the surface charge required for complete adsorption becomes lower as the solvent quality is decreased. Translational diffusion coefficient increases, and the rotational relaxation time decreases as solvent quality is decreased for a fixed surface charge density.

Hydride transfer reaction catalyzed by hyperthermophilic dihydrofolate reductase is dominated by quantum mechanical tunneling and is promoted by both inter- and intramonomeric correlated motions.

J. Pang, Jingzhi Pu, Jiali Gao, D.G. Truhlar, and R.K. Allemann* [Univ. of Minnesota]

J. Am. Chem. Soc. **128** (25), 8015 -8023, 2006.

MD simulations are used to study the hydride and deuteride transfer catalyzed by dihydrofolate reductase from the hyperthermophile Thermotoga maritima (TmDHFR). TmDHFR is modeled with its active homodimeric quaternary structure, where each monomer has three subdomains. The decreased catalytic efficiency of the monomer is not the result of a decrease of the tunneling contribution but an increase in the quasi-classical activation free energy. The catalytic effect is associated in the dimer with correlated motions between domains as well as within and between subunits. The intrasubunit correlated motions are decreased in the monomer when compared to both native dimeric TmDHFR and monomeric *E. coli* enzyme.

Association of transmembrane helices: What determines assembling of a dimer?

R.G. Efremov* [Russian Acad. of Sci.], Y.A. Vereshaga, P.E. Volynsky, D.E. Nolde and A.S. Arseniev.

*J.Comp. Aided Mol.Design.***20**, 27-45 (2006)

MC simulations are applied to study the self-association of two hydrophobic α-helices, described by an effective potential. The influence of TM electrostatic potential, thickness and hydrophobicity degree of lipid bilayer is investigated. It is shown that the membrane environment stabilizes α-helical conformation of GpA monomers, induces their TM insertion and facilitates inter-helical contacts.

QM/MM

Combining quantum mechanics methods with molecular mechanics methods in ONIOM.

Thom Vreven* [Gaussian Inc.], K. Suzie Byun, Istvan Komaromi, Stefan Dapprich, J.A. Montgomery, Jr., Keiji Morokuma, and M.J. Frisch

J.Chem. Theor. and Comp. **2**, 815-826 (2006)

The ONIOM (QM:MM) scheme, the electrostatic interaction between the regions is included at the classical level is presented. The behavior of ONIOM with electronic embedding is more stable than QM/MM with electronic embedding. The link atom correction is investigated, which is implicited in ONIOM but not in QM/MM. The ONIOM(QM:MM) calculations showed the potential surface is discontinuous when there is bond breaking and forming closer than three bonds from the MM region.

Theoretical calculation of hydrogen-bonding strength for drug molecules.

Ming-Hong Hao* [Boehringer Ingelheim Pharma., Inc.]

J.Chem. Theor. and Comp. **2**, 863-872 (2006)

DFT based method is presented to predict the hydrogen-bonding strength for different acceptors with respect to a given donor or vice versa. The results indicated the predictive power of this method but also shed light on factors that determine the magnitude of experimentally measured hydrogen-bonding constants for different acceptors with respect to a given donor. The results suggested a primarily enthalpic contribution from hydrogen-bonding energy. This is useful for evaluating the effects of steric interference and inhibitor binding geometry on hydrogen-bonding strength in drug design.

Computing the amino acid specificity of fluctuations in biomolecular systems.

K. Hamacher* [Univ. of Calif.] and J. A. McCammon

J.Chem. Theor. and Comp. **2**, 873-878 (2006)

A new specification method is developed for the computation of spatial fluctuations of proteins around their native structures. The consistency with experimental values and the increased performance in comparison to an established model, based on statistical estimates for a set of test proteins is showed. We applied the new method to HIV-1 protease in its wild-type form and to a V82F-I84V mutant that shows resistance to protease inhibitors. It was further showed how the method is used to explain the molecular biophysics of drug resistance of the mutant.

The stabilities of N-Cl bonds in biocidal materials.

A. Akdag, S. Okur, M.L. McKee, and S. D. Worley* [Auburn Univ.]

J.Chem. Theor. and Comp. **2**, 879-884 (2006)

B3LYP/6-31+G(d) level is applied and using the conductor-like polarizable continuum aqueous solvation model with UAKS cavities. It is found that the imide and amide N-halamine stabilities on hydantoin rings could be reversed with substitution patterns at the 5 position.

Accurate prediction of the blood-brain partitioning of a large set of solutes using *ab initio* calculations and genetic neural network modeling.

Bahram Hemmateenejad*[Shiraz Univ.], Ramin Miri , Mohammad A. Safarpour , Ahmad R. Mehdipour

J.Comp. Chem. **27,** 1125-1135 (2006)

A genetic algorithm-based artificial neural network model is developed for the accurate prediction of the blood-brain barrier partitioning of chemicals. A data set of 123 log*BB* of a diverse set of chemicals is choosing. The optimum 3D geometry of the molecules is estimated by the *ab initio* calculations at the level of RHF/STO-3G, and different electronic descriptors are calculated for each molecule. The best model produced RMS error of prediction 0.140, and could predict about 98% of variances in the log*BB* data.

QM/MM (cont'd)

A QM/MM study on the aqueous solvation of the tetrahydroxouranylate $[UO_2(OH)_4]^{2-}$ complex ion.

Ivan Infante, Bas van Stralen, and Lucas Visscher* [Vrije Univ. Amsterdam]

J.Comp. Chem. **27,** 1156-1162 (2006)

QM/MM method is applied to study the coordination of the tetrahydroxouranylate ion in aqueous solution. QM/MM geometry optimizations showed that a hexa-coordinated structure is more stable than the hepta-coordinated structure by 43 kJ/mol. Charge transfer of the tetrahydroxouranylate to the solvating water molecules is relatively modest, and is modeled by including a solvation layer consisting of 12 explicit water molecules.

Can the semiempirical PM3 scheme describe iron-containing bioinorganic molecules?

J.P. McNamara, M. Sundararajan, I.H. Hillier* [Univ. of Manchester], Jun Ge, A. Campbell, and C. Morgado

J. Comp. Chem. **27,** 1307-1323 (2006)

B3LYP/6-31G* level for a training set of 60 representative complexes are employed and a gradient-based optimization algorithm is used. The derived parameters lead in general to good predictions of the structure and energetics of molecules both within and outside the training set, and overcome the extensive deficiencies of a B3LYP/STO-3G model. The derived parameter set provides a starting point should greater accuracy for a more restricted range of compounds are required.

QM/MM modeling of compound I active species in cytochrome P450, cytochrome C peroxidase, and ascorbate peroxidase.

Jeremy N. Harvey* [Univ. of Bristol], Christine M. Bathelt, and A.J. Mulholland

J. Comp. Chem. **27***,* 1352-1362 (2006)

QM/MM calculations are applied on Cytochrome *c* Peroxidase (CcP) and Ascorbate Peroxidase (APX) and computational data is presented. The results suggested that the difference in electronic structure is due to a large number of small differences in structure from one protein to another. QM/MM calculations on the active species of cytochrome P450 are discussed, the electronic structure to the environment is found.

QM/MM calculations with DFT for taking into account protein effects on the EPR and optical spectra of metalloproteins. Plastocyanin as a case study.

Sebastian Sinnecker, and Frank Neese*[Planck Inst. for Bio Inorg. Chem.]

J. Comp. Chem. **27***,* 1463-1475 (2006)

QM/MM approach is used to study the influence of the surrounding protein on magnetic and optical spectra of metalloproteins. The calculations are performed using nonrelativistic and scalar relativistic calculations. The best results obtained at the scalar relativistic ZORA level for the largest model in conjunction with explicit modeling of the protein environment through the QM/MM procedure. The protein effects required an explicit treatment of the protein beyond the second coordination sphere.

Quantum chemistry applied to the mechanisms of transition metal containing enzymes - Cytochrome *c* oxidase, a particularly challenging case.

M.R.A. Blomberg* [AlbaNova Univ.], and P.E.M. Siegbahn

J. Comp. Chem. **27***,* 1373-1384 (2006)

DFT with B3LYP level is used to study the mechanisms of O-O bond cleavage and proton pumping in cytochrome c Oxidase. It is possible to construct the models, which are accurately reproduce relative redox potentials and pK_a values within the active site and to calculate energy profiles. The energy between the reductive and oxidative half cycles, which is not correlated with the experimental observation that the proton pumping is evenly distributed between the two half cycles.

QM/MM (cont'd)

An ab initio computational study of thiamin synthesis from gaseous reactants of the interstellar medium.

N. Aylward* [Queensland Univ. of Tech.]

J.Biophys. **122**, 185-193, 2006.

The formation of thiamin derivatives from gaseous reactants is identified in the interstellar medium, and is relevant to a prebiotic atmosphere. The gaseous mixture consisted of methanimine, acetonitrile, cyanoacetylene, ammonia, acetylene, allylene, hydrogen sulfide, thioformaldehyde, and hydrogen in the presence of water. HF and MP2/6-31G* level is used to study the overall enthalpy changes in the ZKE approximation.

Ligand Docking

Artificial transfer hydrogenases based on the biotin-(Strept)avidin technology: Fine tuning the selectivity by saturation mutagenesis of the host protein.

C. Letondor, A. Pordea, Nicolas Humbert, Anita Ivanova, S. Mazurek, M. Novic, and T.R. Ward* [Nat. Inst. Chem.]

J. Am. Chem. Soc. **128** (25), 8320 -8328, 2006

Docking studies are used to choose the genetic optimization site, which reveal that S112 position lies closest to the biotinylated metal upon incorporation into streptavidin. The results suggested that the enantioselection is mostly dictated by CH/π interactions between the substrate and the η^6-bound arene. These enantiodiscriminating interactions are outweighed in the presence of cationic residues at position S112 to afford the opposite enantiomers of the product.

Docking studies of Nickel-Peptide deformylase (PDF) inhibitors: Exploring the new binding pockets.

Q. Wang, D. Zhang, J. Wang, Zhengting Cai* [Shandong Univ.], and Weiren Xu

J.Biophys. 122, 43-49, 2006.

Auto Dock is used to study the binding modes of a series of known activity inhibitors to peptide deformylase (PDF). The results are good agreement with the calculated binding energies and experimental inhibitory activities. It is concluded that some shallow pockets near the known active pocket are important which could accommodate the side-chains of the inhibitor.

Peptide Conformational Analysis

Multiple pathways in conformational transitions of the alanine dipeptide: An application of dynamic importance sampling.

Hyunbum Jang* [Johns Hopkins Univ.], T.B. Woolf

J.Comp. Chem. **27,** 1136-1141 (2006)

Dynamic importance sampling (DIMS) method is used to study the multiple dynamic transition pathways on the two-dimensional dihedral plane between conformational states of the alanine dipeptide. Free energy surfaces on the dihedral plane are calculated from the equilibrium simulations, and four energy minima defined from the surface are used as the starting and ending points for DIMS dynamics, results multiple transition pathways within complex biomolecular systems.

Protein Structure Prediction

Performance of DFT in modeling electronic and structural properties of cobalamins.

Jadwiga Kuta, Seguei Patchkovskii, M.Z. Zgierski, P.M. Kozlowski* [Univ. of Louisville]

J. Comp. Chem. **27***,* 1429-1437 (2006).

The electronic and structural properties of coenzyme B_{12} models are performed to examine the performance of three different functionals including B3LYP, BP86, and revPBE. The cobalt-carbon bond dissociation energies, axial bond lengths, and selected stretching frequencies are analyzed. The results showed that B3LYP functional significantly underestimates the strength of the Co-C bond while the nonhybrid BP86 functional produces very consistent results in comparison to experimental data.

Threading or Fold Prediction

Generalized simulated annealing applied to protein folding studies.

F.P. Agostini* [LNCC], D.De O. Soares-Pinto , M.A. Moret, Carla Osthoff , P.G. Pascutti

J.Comp. Chem. **27,** 1142-1155 (2006)

The Generalized Simulated Annealing method coupled to the GROMOS96 molecular force field is applied to study the minimum energy confirmation of 18-alanine. The q_T GSA parameter is used to control the freezing process during the annealing procedure, and to avoid polypeptide chains to be trapped in energy local minima. Grid computing platform is developed and tested based on MYGRID middleware, which is a technology that is employed all machines accessed by the user to run the application.

***Ab initio* protein fold prediction using evolutionary algorithms: Influence of design and control parameters on performance.**

D.P. Djurdjevic, M.J. Biggs* [Univ. of Edinburgh]

J.Comp. Chem. **27,** 1177-1195 (2006).

The real encoding and multipoint crossover are superior, while both generational and steady-state replacement strategies have merits. The scaling between the optimal control parameter settings and polyalanine size is identified for both generational and steady-state designs based on real encoding and multipoint crossover. The steady-state design to met-enkephalin indicated that these scalings are potentially transferable to real proteins. Comparison of the performance of the steady state design for met-enkephalin with other *ab initio* methods indicates that EAs can be competitive provided the correct design and control parameter values are used.

Molecular Graphics

Small molecule screening by imaging.

U.S. Eggert* [Harvard Med. Sch.] and T.J. Mitchison

Curr. Opi. Stru.Biol. **10**, 232-237, 2006.

The use of model organisms such as zebrafish in screens and review different methods of target identification are discussed. The emerging field of automated image analysis is also introduced.

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

Journal of Computational Chemistry 27(8), August, 2006

1119-1124 **2D representation of protein secondary structure sequences and its applications,** Liwei Liu* [Dalian Univ. of Tech.], T. Wang.

2D representation of protein secondary structure sequences is proposed to display, analyze, and compare the secondary structure sequences.

1125-1135 **Accurate prediction of the blood-brain partitioning of a large set of solutes using ab initio calculations and genetic neural network modeling,** B. Hemmateenejad* [Shiraz Univ.], R. Miri, M.A. Safarpour , A.R. Mehdipour.

A genetic algorithm-based artificial neural network model is developed for the accurate predition of the blood-brain barrier partitioning (in log*BB* scale) of chemicals.

1136-1141 **Multiple pathways in conformational transitions of the alanine dipeptide: An application of dynamic importance sampling,** Hyunbum Jang*[Johns Hopkins Univ.], T.B.Woolf

Dynamic importance sampling (DIMS) method with unbiased MD simulations are used to generate equilibrium ensembles for the alanine dipeptide within different states.

1142-1155 **Generalized simulated annealing applied to protein folding studies**, Flavia P. Agostini* [Lab. of Nati. Compu. Cent.], Diogo De O. Soares-Pinto, Marcelo A. Moret, Carla Osthoff, Pedro G. Pascutti.

The Generalized Simulated Annealing method coupled to the GROMOS96 molecular force field is applied. The q_T GSA parameter is used to control the freezing process during the annealing procedure, and to avoid polypeptide chains to be trapped in energy local minima.

1156-1162 **A QM/MM study on the aqueous solvation of the tetrahydroxouranylate $[UO_2(OH)_4]^{2-}$ complex ion,** Ivan Infante, Bas van Stralen, Lucas Visscher * [Vrije Univ. Amsterdam]

QM/MM study on the coordination of the tetrahydroxouranylate ion in aqueous solution is reported.

1163-1176 **A multiple time step algorithm compatible with a large number of distance classes and an arbitrary distance dependence of the time step size for the fast evaluation of nonbonded interactions in molecular simulations,** Vincent Kräutler, P.H. Hünenberger*[

A new algorithm is introduced to perform the multiple time step integration of the equations of motion for a molecular system, based on the splitting of the nonbonded interactions into a series of distance classes.

1177-1195 ***Ab initio* protein fold prediction using evolutionary algorithms: Influence of design and control parameters on performance,** Dusan P. Djurdjevic and Mark J Biggs* [Univ. of Ediburgh]

Comparison of the performance of the steady state design for met-enkephalin with other *ab initio* methods indicates that EAs could be competitive provided the correct design and control parameter values are used.

1196-1202 **Coronavirus phylogeny based on 2D graphical representation of DNA sequence,** Bo Liao* [Hunan Univ.], Xuyu Xiang, Wen Zhu

A new approach is proposed based on the 2D graphical representation of the whole genome sequence to analyze the phylogenetic relationships of coronaviruses.

1203-1210 **A new approach to counterpoise correction to BSSE**, Annia Galano* [Inst. Mexican Petroleum], J. Raúl Alvarez-Idaboy.

The intermolecular BSSE is obtained by subtracting the intramolecular BSSE of the fragments from the intramolecular BSSE of the supermolecule, and considering every atom as a fragment in the calculation of each intramolecular BSSE.

1211-1219 **Simulation of phase separation in alcohol/water mixtures using two-body force field and standard molecular dynamics,** E.S. Ferrari, R.C. Burton , R.J. Davey*[The Univ. of Manchester], A.G.R.J. Davey

MD simulations are carried out, All-atom force field with Lennard-Jones potentials are used for mixtures by developing combination rules with the TIP3P water model.

Journal of Computational Chemistry 27(9), September, 2006

1223-1229 **Spin states in polynuclear clusters: The [Fe_2O_2] core of the methane monooxygenase active site,** Carmen Herrmann, Lian Yu, Markus Reiher*[Lab. for Phys.Chem.]

The energetics of different total and local spin states of a dinuclear oxygen-bridged iron(IV) model for the intermediate Q of the hydroxylase component of methane monooxygenase by means of spin-unrestricted Kohn-Sham density functional theory.

1240-1262 **Quantum mechanical and molecular dynamics simulations of ureases and Zn β-lactamases,** Guillermina Estiu, Dimas Suárez, Kenneth M. Merz, Jr * [Univ. of Florida]

QM/MM and MD simulations are applied to describe the structure and function of metallo-β-lactamases and ureases.

1263-1277 **DFT models for copper(II) bispidine complexes: Structures, stabilities, isomerism, spin distribution, and spectroscopy,** Mihail Atanasov , Peter Comba* [Univ. of Heidelberg], Bodo Martin , Vera Müller, Gopalan Rajaraman, Heidi Rohwer , Steffen Wunderlich

A*b initio* methods, including B3LYP, HF, SORCI, and LF-density functional theory (DFT), are used to compute the structures, relative stabilities, spin density distributions, and spectroscopic properties of the two possible isomers of the copper(II) complexes with derivatives of a rigid tetradentate bispidine ligand with two pyridine and two tertiary amine donors, and a chloride ion.

1278-1291 **Theoretical, spectroscopic, and mechanistic studies on transition-metal dinitrogen complexes: Implications to reactivity and relevance to the nitrogenase problem,** Felix Studt, Felix Tuczek* [Christian-Albrechts-Univ.]

DFT calculations are used to investigate the dinitrogen complexes of transition metals exhibit different binding geometries of N_2.

1292-1306 **DFT calculations of 57Fe Mössbauer isomer shifts and quadrupole splittings for iron complexes in polar dielectric media: Applications to methane monooxygenase and ribonucleotide reductase**, Wen-Ge Han, Tiqing Liu, Timothy Lovell, Louis Noodleman*[The Scripps Res.Inst.]

The geometries and electronic structures of all complexes in the training sets are optimized within the conductor like screening (COSMO) solvation model.

1307-1323 **Can the semiempirical PM3 scheme describe iron-containing bioinorganic molecules?** J.P. McNamara, M. Sundararajan, I.H. Hillier* [Univ. of Manchester], Jun Ge, A. Campbell, C. Morgado

The semiempirical PM3 method have been developed to allow the structure and redox properties of the active sites of iron-containing proteins to be accurately modeled, focussing on iron-sulfur, iron-heme, and iron-only hydrogenases.

1352-1362 **QM/MM modeling of compound I active species in cytochrome P450, cytochrome C peroxidase, and ascorbate peroxidase,** J.N. Harvey* [Univ. of Bristol], C.M. Bathelt, A.J. Mulholland

QM/MM calculations are applied on Cytochrome *c* Peroxidase (CcP) and Ascorbate Peroxidase (APX) and computational data is presented.

1363-1372 **On the O_2 binding of Fe-porphyrin, Fe-porphycene, and Fe-corrphycene complexes,** H. Nakasima, Jun-ya Hasegawa, H. Nakatsuji* [Kyoto Univ.]

The O_2 binding mechanism in the Fe-porphyrin isomers, Fe-porphycene (FePc), and Fe-corrphycene (FeCor) complexes are investigated.

1373-1384 **Quantum chemistry applied to the mechanisms of transition metal containing enzymes – Cytochrome *c* oxidase, a particularly challenging case,** M.R.A. Blomberg* [AlbaNova Univ. Cent. Stockholm Univ.] , P.E. M. Siegbahn.

DFT with B3LYP level is used to study the mechanisms of O-O bond cleavage and proton pumping in cytochrome c Oxidase.

1385-1397 **On the accuracy of density functional theory for iron - sulfur clusters,** R.K. Szilagyi* [Montana State Univ.], and M.A. Winslow.

A simple wave function method is demonstrated for developing ground state electronic wave function for [2Fe-2S] and [Mo-3Fe-4S] clusters.

1398-1414 **The reaction mechanism of iron and manganese superoxide dismutases studied by theoretical calculations,** Lubomír Rulíšek, Kasper P. Jensen, Kristoffer Lundgren, Ulf Ryde* [Lund Univ.]

The reaction mechanism of iron and manganese superoxide dismutase with DFT calculations on realistic active-site models, with large basis sets and including solvation, zero-point, and thermal effects are investigated.

1415-1428 **Metal-thiolate bonds in bioinorganic chemistry,** E.I. Solomon* [Stanford Univ.], S.I. Gorelsky, Abhishek Dey.

The energy of the metal-thiolate bond is fairly insensitive to its ionic/covalent and π/σ nature as increasing M-S covalency reduces the charge distribution, hence the ionic term, and these contributions could compensate.

1429-1437 **Performance of DFT in modeling electronic and structural properties of cobalamins,** Jadwiga Kuta, Seguei Patchkovskii, M.Z. Zgierski, P.M. Kozlowski* [Univ. of Louisville]

The electronic and structural properties of coenzyme B_{12} models are performed to establish the performance of three different functionals including B3LYP, BP86, and revPBE.

1438-1445 **A DFT study of the mechanism of Ni superoxide dismutase (NiSOD): Role of the active site cysteine-6 residue in the oxidative half-reaction,** Rajeev Prabhakar, Keiji Morokuma* [Emory Univ.], Djamaladdin G. Musaev.

DFT study, the catalytic mechanism of H_2O_2 formation in the oxidative half-reaction of NiSOD, E-Ni(II) + O_2^- + $2H^+$ ⟶ E-Ni(III) + H_2O_2 is investigated.

1446-1453 **A DFT study on the relative affinity for oxygen of the α and β-subunits of hemoglobin,** Jean-Didier Maréchal, F. Maseras* [Inst. of Chem.Res. of Catalonia], A. Lledós, L. Mouawad, D. Perahia.

DFT calculations are performed on computational models of the active center of the α- and β-subunits of hemoglobin in both its oxygenated (R) and deoxygenated (T) states.

1454-1462 **Correlation between computed gas-phase and experimentally determined solution-phase infrared spectra: Models of the iron-iron hydrogenase enzyme active site,** J.W. Tye, M.Y. Darensbourg, M.B. Hall* [Texas A&M Univ.]

Gas-phase DFT calculations with double zeta plus polarization basis sets are used to predict the solution-phase infrared spectra for a series of CO- and CN-containing iron complexes.

1463-1475 **QM/MM calculations with DFT for taking into account protein effects on the EPR and optical spectra of metalloproteins: Plastocyanin as a case study,** S. Sinnecker, Frank Neese*[Planck-Inst. for Bio-Inorg. Chem.]

QM/MM approach is used to study the influence of the surrounding protein on magnetic and optical spectra of metalloproteins.

Theoritical Chemistry Accounts: Theory, Computation and Modeling, 115(5), 2006

343-347 **Assignment of the first photoelectron band of $CH_3CHBr(X^2A)$ using Ab-initio an density functional theory (DFT) computational calculations**, M.H.N. Zamanpour* [Teacher Training Univ.] and G. Ebrahimzadeh

ΔSCF, ΔMP2 (full) and Δ(B3LYP) methods are used with different basis sets to calculate the vertical ionization energies were computed in this work for $CH_3CHBr(X^2A)$ and $CH_2CH_2Br(X^2A)$.

348-353 **On the nature of oxoiron (IV) intermediate in dioxygen activation by non-heme enzymes**, A.V. Nemukhin, I.A. Topol* [Nat. Cancer Inst. at Frederick], R.E. Cachau and S.K. Burt.

Electronic properties of the molecular systems with the short distance Fe-O unit, which are presumably formed as reaction intermediates during oxygen activation by non-heme enzymes.

354-360 **Analytical Hartree-Fock gradients with respect to the cell parameter: systems periodic in one and two dimensions**, K. Doll*[Inst. of Math.Phys.], R. Dovesi and R. Orlando.

Hartree-Fock gradients with respect to the cell parameter are implemented in the electronic structure code CRYSTAL, for the case of one- and two-dimensional periodicity expressed in Gaussian type orbitals.

361-369 **Structural and electronic characterization of antioxidants from marine organisms**, M. Belcastro, T.Marino and N. Russo* [Univ. of Calabria] and M. Toscano

DFT with B3LYP/6-311++G** level is used to investigate the molecular properties of new systems that serve as antioxidants.

4. ADDRESSES OF PRINCIPAL AUTHORS

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

Abderrazzak Douhal
Dept. de Química Física
Sección de Químicas
Facu. of Chem. del Med. Ambiente
Univ. de Castilla-La Mancha
Avda. Carlos III, S.N., 45071
Toledo, Spain

Anne Charrier
Cent. de Res. en Mat. Cond. et Nanosci.
Cent. Nati. la Res. Sci.
Univ. de la Méditerranée
Marseille, France

Annia Galano
agalano@imp.mx
Inst. Mexicano del Petróleo
Eje Central Lázaro Cárdenas 152
007730 México D.F.
México

Arun Yethiraj
Dept. of Chem.
Kwangwoon Univ.
Seoul, 139-701
Republic of Korea

Arto Urtti
Drug Discov. & Develop., Phys. Chem. & Pharmacokinetic Simulations
Orion Pharma
P.O. Box 65, FIN-02101 Espoo
Finland

Bahram Hemmateenejad
hemmatb@sums.ac.ir
Dept. of Chem.
Shiraz Univ.
Shiraz, Iran

G. Berthier
berthier@lct.jussieu.fr
Lab. de Chem. Théor.
Univ. at Pierre et Marie Curie
CNRS-UMR 7616, Case 137
4 place Jussieu
75252 Paris Cedex 05
France

Bo Liao
dragonbw@163.com
Lab. of Embedded Compu. and System
Sch. of Comp. and Commun.
Hunan Univ.
Changsha Hunan 410082
PR China

Bahram Hemmateenejad
hemmatb@sums.ac.ir
Dept. of Chem.
Shiraz Univ., Shiraz
Iran

B. J. Berne
Dept. of Chem.
Columbia Univ.
3000 Broadway, New York
New York 10027
U.S.A.

Beenu Moza
sundberg@bbri.org
Boston Biomed. Res. Inst.
Watertown, MA 02472
U.S.A.

H.A. Carlson
Biophys. Res. Division
930 North Univ.
Univ. of Michigan
Ann Arbor, Michigan 48109-1055
USA

Carlos Alemán
carlos.aleman@upc.es
Dept. of Engg. Quím.
E.T.S. d'Enginyers Industrials de Barcelona
Univ. at Politécnica de Catalunya
Diagonal 647, E-08028 Barcelona
Spain

Christoph Rücker
Biocenter
Univ. of Basel,
Klingelbergstrasse 50-70
CH-4056 Basel
Switzerland

Claudiu T. Supuran
claudiu.supuran@unifi.it
Univ. degli Stud. di Firenze
Polo Sci., Lab. di Chim. Bioinorg.
Rm. 188, Via della Lastruccia 3
50019 Sesto Fiorentino (Florence)
Italy

L. P. Cavalcanti
cavalcanti@esrf.fr
Euro. Synchrotron Radiation Facility (ESRF)
Grenoble Cedex
France

Christoph Alexiou
C.Alexiou@web.de
Klinik und Poliklinik für Hals-Nasen- Ohren- kranke
Univ. Erlangen – Nürnberg
Erlangen, Germany

Colin W. Glass
Lab. of Crystallography
Dept. of Materials
ETH Zurich, HCI G 515
Wolfgang-Pauli-Strasse 10
CH-8093 Zurich
Switzerland

Cecilia Clementi
cecilia@rice.edu
Stru. and Compu. Biol. and Mol. Biophys.
Baylor Coll. of Medicine
Houston, TX 77030
USA

S.-H. Chen
sowhsin@mit.edu
Dept. of Nuclear Sci. and Engg.
Massachusetts Inst. of Tech.
Cambridge, MA 02139
U.S.A.

R. J. Davey
roger.davey@manchester.ac.uk
Sch. of Chem. Engg. and Analytical Sci.
The Univ. of Manchester
P.O. Box 88, Manchester M60 1QD, UK

David Swigon
swigon@pitt.edu
Dept. of Chem. and Chem. Biol. and Mech. and Mat.Sci.
Rutgers, The State Univ. of New Jersey
Piscataway, NJ 08854
USA

B. David Silverman
silverma@us.ibm.com
IBM Thomas J. Watson Research Center
P. O. Box 218
Yorktown Heights, NY 10598
U.S.A.

Douglas H Turner
Dept. of Chem.
Univ. of Rochester
Rochester, NY 14627-0216
USA

Edward E. Knaus
Facu. of Pharm. and Pharm.Sci.
Univ. of Alberta
Edmonton, Alta., Canada T6G 2N8

A.D. Ellington
Univ. of Texas at Austin
1 University Station
A4800, Austin, TX 78712, USA

Edward N. Trifonov
trifonov@research.haifa.ac.il
Res. Inst. for Biol. Resources and Functions
Nat. Inst. of Adv. Industr. Sci. and Tech.
1-1-1 Higashi Tsukuba
Ibaraki 305-8566, Japan

Edward I. Solomon
Edward.Solomon@stanford.edu
Dept. of Chem.
Stanford Univ.
333 Campus Drive
Stanford, California 94305
USA

Edward N. Brothers
Dept. of Chem.
Mail Stop 60, Rice Univ.
Houston, Texas 77005-1892
USA.

Flavia P. Agostini
flavia@lncc.br
Lab. Nati. Compu. Cent. – LNCC
Petrópolis, Rio de Janeiro, Brazil

Felix Tuczek
ftuczek@ac.uni-kiel.de
Inst. für Anorganische Chem.
Christian-Albrechts-Univ. Kiel
Otto Hahn Platz 6/7, 24098 Kiel
Germany

J.D. Faraldo-Gómez
mark.sansom@bioch.ox.ac.uk
Dept. of Biochem.
Univ. of Oxford
South Parks Road, Oxford OX1 3QU, UK.

Feliu Maseras
fmaseras@iciq.es
Inst. of Chem. Res. of Catalonia (ICIQ)
43007 Tarragona, Catalonia
Spain

Flavia P. Agostini
flavia@lncc.br
Lab. Nati. de Comp. Cent. – LNCC
Petrópolis, Rio de Janeiro
Brazil

Frank L. H. Brown
Dept. of Chem. and Biochem.
Univ. of California
Santa Barbara
California 93106-9510
USA

Frank Neese
theochem@thch.uni-bonn.de
Max-Planck-Inst. for Bio-Inorg. Chem.
Stiftstrasse 34-36, D-45470
Mülheim an der Ruhr
Germany

Geert-Jan Boons
gjboons@ccrc.uga.edu
Ontario Cancer Inst. and Dept. of Med. Biophys.
Univ. of Toronto
101 College Street
Toronto, Ontario
Canada M5G 1L7

Giulio Vistoli
Istituto di Chimica Farma.
Facu. di Farmacia
Univ. di Milano
Viale Abruzzi 42
I-20131 Milano, Italy

Gregory A. Voth
Dept. of Chem. and Cent. for Biophys. Model. and Simulation
Univ. of Utah
315 South 1400 East Room 2020
Salt Lake City, Utah 84112-0850
USA

Giulio Vistoli
Inst. of Chem. Pharrma.
Facu. di Pharm.
Univ. di Milano
Viale Abruzzi 42, I-20131 Milano
Italy

K. Hamacher
Howard Hughes Medical Inst.
Univ. of California at San Diego
La Jolla, California 92093-0365

S. Hammes-Schiffer
Dept. of Chem.
Pennsylvania State Univ.
Univ. Park, Pennsylvania 16802
U.S.A.

Haralambos Sarimveis
hsarimv@central.ntua.gr
Sch. of Chem. Engg.
Nati. Tech. Univ. of Athens
Athens, Greece

Harold A. Scheraga
Facu. of Chem.
Univ. of Gdansk
Sobieskiego 18
80-952 Gdansk, Poland

J.-P. Hénichart
Univ. de Lille-II
rue du professeur-Laguesse
BP 83, 59006 Lille
France

Hervé Duclohier
herve.duclohier@univ-poitiers.fr
Inst. de Physiol. et de Biol. Cellulaires (Pôle Biologie Santé), UMR 6187 CNRS-Univ. de Poitiers
40 Avenue du Recteur Pineau
86022 Poitiers, France

Hirotaka Ode
odehir@graduate.chiba-u.jp
Graduate School of Pharma.Sci.
Chiba Univ.
Chiba 263-8522, Japan

Hiroshi Nakatsuji
hiroshi@sbchem.kyoto-u.ac.jp
Dept. of Synthetic Chem. and Biol. Chem.
Graduate Sch. of Engg.
Kyoto Univ.
Katsura, Nishikyo-ku, Kyoto 615-8510
Japan

Hyunbum Jang
jangh@ncifcrf.gov
Department of Physiology
Johns Hopkins University
Baltimore, Maryland 21205
USA

Ian H. Hillier
Ian.Hillier@manchester.ac.uk
School of Chem.
Univ. of Manchester
Manchester, M13 9PL
United Kingdom

Igor A. Topol
topol@ncifcrf.gov
Advanced Biomed. Comp. Cent.
Nati. Cancer Inst. at Frederick
Frederick, MD 21702, USA

Jack W. Szostak
szostak@molbio.mgh.harvard.edu
Dept. of Mol.Biol., and Cent. for Comp. and Integrative Biol.
7215, Simches Res. Cent.
Massachusetts General Hospital
185 Cambridge Street, Boston
Massachusetts 02114

Jan Ziegler
jan.ziegler@uni-bayreuth.de
Lehrstuhl Biopolymere
Univ. of Bayreuth,
Universitätsstr. 30
95444 Bayreuth
Germany

Jeremy N. Harvey
Jeremy.Harvey@bristol.ac.uk
School of Chem. and Cent. for Comp.Chem.
Univ. of Bristol
Cantock's Close, Bristol BS8 1TS
United Kingdom

Jean-Pierre Dognon
Lab. de Chem. et Phys. Quantiques
IRSAMC, Univ. Paul Sabatier
118 Route de Narbonne
F31062 Toulouse Cedex
France

Jon S Thorson
Lab. for Biosynthetic Chem., Pharm. Sci.
Sch. of Pharmacy
Univ. of Wisconsin-Madison
777 Highland Avenue, Madison
Wisconsin 53705, USA

Kapil Mayawala
Dept. of Chem. Engg.
150 Academy Street
Univ. of Delaware
Newark, DE 19716, USA

Kazuhisa Nishizawa
kazunet@med.teikyo-u.ac.jp
Dept. of Biochem.
Sch. of Med., Teikyo Univ.
Kaga, Itabashi, 173-8605 Tokyo
Japan

A. Karpfen
JC.Sancho@ua.es
Dept. de Química Física
Univ. de Alicante, 03080 Alicante
Spain

Keiji Morokuma
morokuma@emory.edu
Cherry L. Emerson Cent. for Sci. Comp. & Dept. of Chem.
Emory Univ.
1515 Dickey Dr., Atlanta, Georgia 30322

Kenneth M. Merz, Jr
merz@qtp.ufl.edu.
Dept. of Chem.
Quantum Theory Project
Univ. of Florida
2328 New Physics Building
P.O. Box 118435
Gainesville
Florida 32611-8435

Leonid Yelash
Inst. for Phys., WA 331
Johannes-Gutenberg Univ. at Mainz
Staudingerweg 7
D-55099 Mainz, Germany

Liwei Liu
daliguowei@163.com
Dept. of Applied Mathematics
Dalian Univ. of Tech.
Dalian 116024
PR China

Louis Noodleman
lou@scripps.edu
Dept. of Mol. Biol.
TPC15, The Scripps Res. Inst.
10550 N. Torrey Pines Road
La Jolla, California 92037

Lucas Visscher
visscher@chem.vu.nl
Theor. Chem. Section
Facu. of Sci.
Vrije Univ. Amsterdam
De Boelelaan 1083
1081 HV Amsterdam
The Netherlands

R. Malathi
r_malathi@hotmail.com
Dept. of Med.
Univ. of Tennessee
Health Sci. Cent.
874 Union Avenue
Memphis, Tennessee- 38163, USA

Maoxiang Wang
Nat. Lab. of Solid State Microstructures
Dept. of Phys.
Nanjing Univ.
Nanjing 210093, China

Maria Letizia Barreca
Dept. of Pharma-Chem.
Univ. di Messina
Viale Annunziata, 98168 Messina, Italy

Maurizio Botta
Inst. di Genetica Molecolare
IGM-CNR, Via Abbiategrasso 207
I-27100, Pavia
Italy.

Margareta R. A. Blomberg
mb@physto.se
Dept. of Physics
AlbaNova Univ. Center
Stockholm University
S-106 91 Stockholm
Sweden

Mark J. Biggs
M.Biggs@ed.ac.uk
Inst. for Mat. and Processes
Univ. of Edinburgh
King's Buildings
Mayfield Road
Edinburgh EH9 3JL
United Kingdom

Matthew B Francis
Materials Sciences Division
Lawrence Berkeley Nationals Labs
Berkeley, CA 94720, USA

Masataka Shoji
Pharm. Res. Lab.
Ajinomoto company Inc.
1-1, Suzuki-cho
Kawasaki-ku
Kawasaki-shi
Japan

Mats Larhed
Organic Pharm.Chem.
Dept. of Med.Chem.
Uppsala Univ.
BMC, Box 574, SE-751 23
Uppsala
Sweden

Martin G. Grigorov
martin.grigorov@ rdls.nestle.com
Bioinformatics Center
College of Biological Science
China Agri. Univ.
100094 Beijing, China

Mark S. Gordon
mark@si.fi.ameslab.gov
Dept. of Chem.
Iowa State Univ.
Ames, IA 50011, USA

Mark J. Biggs
M.Biggs@ed.ac.uk
Inst. for Materials and Processes
Univ. of Edinburgh, King's Buildings
Mayfield Road, Edinburgh EH9 3JL, United Kingdom

Markus Reiher
markus.reiher@phys.chem.ethz.ch
Lab. for Phys.Chem.
ETH Zurich, Hoenggerberg
Wolfgang-Pauli-Str. 10, CH 8093 Zurich
Switzerland

Margareta R. A. Blomberg
mb@physto.se
Dept. of Phys.
AlbaNova Univ. Cent. Stockholm Univ.
S-106 91 Stockholm, Sweden

Michael B. Hall
mbhall@tamu.edu
Michael B. Hall, Dept. of Chem.
Texas A&M Univ.
College Station, Texas 77843-3255

Michael L. McKee
Dept. of Chem. and Biochem.
Auburn Univ.
Auburn, Alabama 36849

Miguel José-Yacamán
Chem. Engg. Dept. and Texas Advanced Mat. Cent.
The Univ. of Texas at Austin
Austin, Texas 78712.

Mihaly Mezei
mezei@inka.mssm.edu
Dept. of Physiology and Biophysics
Mount Sinai School of Medicine
NYU, One Gustave L. Levy Place
Box 1218, New York, NY 10029
USA

Ming-Hong Hao
Dept. of Med. Chem.
Boehringer Ingelheim Pharm.Inc.,
Ridgefield, Connecticut 06877
USA

Nikos G. Oikonomakos
Inst. of Org. and Pharm. Chem.
The National Hellenic Research Foundation
48, Vas. Constantinou Ave.
116 35 Athens, Greece

Nino Russo
nrusso@unical.it
Dept. of Chem. and Cent. of Calcolo ad Alte Prestazioni per Elabo. Parallele e Distribuite-Cent. d'Eccellenza MIUR
Univ. della Calabria
87030 Arcavacata di Rende (CS)
Italy

Nigel Aylward
Sch. of Phys. and Chem. Sci.
Queensland Univ. of Tech.
George St., Brisbane
Queensland 4000, Australia

Oren M. Becker
Predix Pharma. Ltd.
3 Hayetzira Street
Ramat Gan 52521, Israel

Pawel M. Kozlowski
pawel@louisville.edu
Dept. of Chem.
Univ. of Louisville, 2320 S. Brook Street, Louisville, Kentucky 40292
USA

Peter G. Wolynes
Dept. of Chem.
Univ. of Illinois
Urbana-Champaign
600 South Mathews Avenue
Urbana, Illinois 61801
USA

Pemra Doruker
doruker@boun.edu.tr
Dept. of Chem. Engg. and Polymer Res. Cent.
Bogazici Univ.
Bebek 34342, Istanbul
Turkey

Peter Comba
peter.comba@aci.uni-heidelberg.de
Univ. Heidelberg
Anorganisch-Chem. Inst.
Im Neuenheimer Feld 270
D-69120 Heidelberg
Germany

Philippe H. Hünenberger
phil@igc.phys.chem.ethz.ch
Philippe H. Hünenberger
Lab. of Phys.Chem.
Wolfgang-Pauli Strasse 10
HC1 G233, ETH-Hoenggerberg
CH-8093 Zürich, Switzerland

Pilar Redondo
Dept. of Quím. Física
Facu. de Ciencias
Univ. de Valladolid
47005 Valladolid, Spain

Prasad V. Bharatam
pvbharatam@niper.ac.in
Dept. of Med. Chem.
Nati. Inst. of Pharma. Edu. and Res. (NIPER)
S.A.S. Nagar, 160 062 Mohali
Punjab, India

René Thomsen
Molegro ApS
Hoegh-Guldbergs Gade 10
Bldg. 1090, DK-8000 Aarhus

Robert L. Jernigan
Dept. of Biochem., Biophys., and Mol. Biol. and Bioinfo. and Compu. Biol. Program
Iowa State Univ.
Ames, Iowa 50011

Roman Lesyk
Dept. of Pharm., Organic and Bioorganic Chem.
Danylo Halytsky Lviv Nat.Med. Univ.
Pekarska 69, Lviv 79010, Ukraine

Rudolf K. Allemann
allemannrk@cardiff.ac.uk
Dept. of Chem. and Supercomp. Inst.
Univ. of Minnesota
207 Pleasant Street S.E.,
Minneapolis, Minnesota 55455-0431, U.S.A.

Roman G. Efremov
efremov@nmr.ru
M.M. Shemyakin and Yu.A. Ovchinnikov Inst. of Bioorg. Chem. Russian Acad. of Sci.
Ul. Miklukho-Maklaya, 16/10, V-437
117997 GSP Moscow, Russia

Robert K. Szilagyi
Szilagy@Montana.edu
Dept. of Chem. and Biochem.
Montana State Univ.
223 Gaines Hall, Bozeman
Montana 59717

Siavosh Mahboobi
Inst. of Pharm.
Facu. of Chem. and Pharm.
Univ. of Regensburg,
D-93040 Regensburg
Germany

Stefano Banfi
Dept. of Stru. and Funct. Biol.
Univ. of Insubria
Via H. Dunant 3
21100 Varese (VA)
Italy

S.A. Strobel
Dept. of Mol. Biophys. & Biochem.
Yale Univ.
260 Whitney Avenue
New Haven, CT 06520-8114
USA

Stephen C. Harvey
School of Biology
Georgia Inst. of Tech.
310 Ferst Drive
Atlanta, Georgia 30332

Stefan Fischer
Compu. Biochem.
Interdisciplinary Cent. for Scientific Computing (IWR)
Univ. of Heidelberg
Im Neuenheimer Feld 368
69120 Heidelberg, Germany

Stephanie L. Brock
sbrock@chem.wayne.edu
Dept. of Chem.
Wayne State Univ.
Detroit, Michigan 48202
USA

Teresa Head-Gordon
Dept. of Bioengg.
Univ. of California, Berkeley
Berkeley, California 94720
USA

Thierry Langer
Dept. of Nephrology and Hypertension
Dept. of Clinical Research
Univ. of Berne
Freiburgstrasse 15
3010 Berne, Switzerland

Thom Vreven
Gaussian, Inc.
340 Quinnipiac Street
Building 40, Wallingford
Connecticut 06492
U.S.A.

Thomas Balle
Danish Univ. of Pharm. Sci.
2 Universitetsparken
DK-2100 Copenhagen
Denmark

Thomas R. Ward
thomas.ward@unine.ch
Laboratory of Chemometrics
Nati. Inst. of Chem.
Hajdrihova 19
SI-1001 Ljubljana
Slovenia

Thy-Hou Lin
Div. of Biotech. & Pharm.Res.
Nati. Health Res. Inst.
35 Keyan Road, Zhunan Town
Miaoli County 350, Taiwan
Republic of China

Ulrike S Eggert
Dept. of Systems Biol.
Harvard Med. Sch.
Boston, MA 02115, USA

Ulf Ryde
Ulf.Ryde@teokem.lu.se
Dept. of Theor. Chem.
Chemical Centre, P.O. Box 124
Lund Univ.
S 221 00, Lund, Sweden

Ursula Schulze-Gahmen
Phys. Biosci. Div. at Lawrence Berkeley Nati. Lab.
1 Cyclotron Road, MS3
Berkeley, California
U.S.A.

Valery V. Malev
valery@vm5692.spb.edu
St. Petersburg State Univ.
Petergof, 198504, Russia

Vincenzo Calderone
Dept. di Psichiatria, Neurobiologia, Pharma. & Biotech.
Università di Pisa
via Bonanno 6, I-56126 Pisa
Italy

Wanda P. Almeida
Dept. of Pharmacology
Facu. Med. Sci./Unicamp
PO Box 6614, 13083-970
Campinas, SP, Brazil

Wing Hung Wong
Dept. of Statistics
Sequoia Hall
Stanford Univ.
Stanford, California 94305
U.S.A.

S. D. Worley
Dept. of Chem. & Biochem.
Auburn Univ.
Auburn, Alabama 36849

Xiaoning Yang
Key Lab. of Mat.-Orientated Chem. Engg. of Jiangsu Province
Coll. of Chem. & Chem.Engg.
Nanjing Univ. of Technology
Nanjing 210009
PR China

Ye Che
chey@nhlbi.nih.gov
Lab. of Comp. Biol.
National Heart, Lung and Blood Inst.
Nati. Inst. of Health
Bethesda, MD 20892
U.S.A.

Yan Alexander Wang
Dept. of Chem.
Univ. of British Columbia
Vancouver, BC V6T 1Z1, Canada

Yang Liu, Xu-Ri Huang
quanchemly@yahoo.com.cn
State Key Lab. of Theor. and Comp.Chem.
Inst. of Theor. Chem.
Jilin Univ.
Changchun, 130023
PR China

Zhengting Cai
Inst. of Theor. Chem.
Shandong Univ.
Jinan 250100, China

Zhang Ruisheng
liumc@lzu.edu.cn
Dept. of Comp. Sci.
Lanzhou Univ.
730000 Lanzhou
China

Ziwei Huang
The Burnham Inst. for Med. Res.
La Jolla, CA 92037, USA

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Editor:

R.Nageswar Ph.D. Tel. (858) 663-0162
MMCC Results E-mail: drnageswar@yahoo.com
RR Labs Inc.,
8013 Los Sabalos Street
San Diego, CA 92126