Results

MOLECULAR MODELING & COMPUTATIONAL CHEMISTRY

Editorial and News

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

     I would call your attention on few highlighted articles, particularly in the Methodology section related to potentials and parameters.

               R.Nageswar, Editor

1. <u>APPLICATIONS</u>

1.1.   *Small Molecules*

General and Model Systems

Crystal structure of the SOCS2-elongin C-elongin B complex defines a prototypical SOCS box ubiquitin ligase.

A.N. Bullock, J.É. Debreczeni, A.M. Edwards, M. Sundström, and Stefan Knapp* [Univ. of Toronto]

PNAS. **103,** 7637-7642 (2006)

The structural basis for SOCS2 function is elucidated and determined the 1.9-Å crystal structure of the ternary complex of SOCS2 with elongin C and elongin B. The structure defines a prototypical SOCS box ubiquitin ligase with a Src homology 2 (SH2) domain as a substrate recognition motif. The SOCS box and SH2 domain showed a conserved spatial domain arrangement with the BC box and substrate recognition domain of the von Hippel-Lindau tumor suppressor protein. The SOCS box binds elongin BC in a similar fashion to the VHL BC box and shows extended structural conservation with the F box of the Skp2 ubiquitin ligase.

Water and Solvation

Water-induced interactions between carbon nano-particles.

Liwei Li, Dmitry Bedrov, and Grant D. Smith* [Univ. of Utah]

J. Phys. Chem. B. **110**, 10509 -10513 (2006)

MD simulations are used to study the hydration of C_{60} fullerenes, carbon nanotubes, and graphene sheets in aqueous solution and the nature of water-induced interactions between these carbon nanoparticles. The hydration of these nonpolar carbon nanoparticles does not exhibit classical hydrophobic character due to the high density of surface atoms resulting in strong water-surface dispersion interactions. Water was found to wet the nanoparticle surfaces independent of nanoparticle surface curvature, with the decrease in the extent of water-water hydrogen bonding with decreasing surface curvature being offset by stronger water-surface interactions.

Solvation in supercritical water.

Jinsong Duan* [Carnegie Mellon Univ.], Y. Shim, and Hyung J. Kim

*J. Chem.Phys.***124**, 204504 - 204516 (2006)

MD simulations are used to study the solvation in super critical water under equilibrium and non-equilibrium conditions. The influence of solute charge distributions and solvent density on the solvation structures and dynamics is examined with a diatomic probe solute molecule. It is observed that the solvation structure varies with the solute dipole moment.

Medicinal Chemistry and Drug Design

Evaluation of glycolamide esters of indomethacin as potential cyclooxygenase-2 (COX-2) inhibitors.

S. Khanna, M. Madan, A. Vangoori, R. Banerjee, R.Thaimattam, S.K. Jafar Sadik Basha, M. Ramesh, Seshagiri Rao and Manojit Pal* [Dr. Reddy's Labs Ltd]

Bioorg. Med. Chem. **14**, 4820-4833 (2006)

A number of novel indomethacin glycolamide esters are tested for their cyclooxygenase inhibition in vitro properties. Many compounds proved to be selective COX-2 inhibitors, and subtle structural changes in the substituents on the glycolamide ester moiety altered the inhibitory properties. Molecular modeling studies are used to rationalize their in vitro data and [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid 2-morpholin-4-yl-2-oxo ethyl ester, is identified as a promising compound.

Synthesis, docking, and in vitro activity of thiosemicarbazones, aminoacyl-thiosemicarbazides and acyl-thiazolidones against Trypanosoma cruzi.

A.C. Lima Leite* [Univ. Federal de Pernambuco], R.S. de Lima, D.R. de M. Moreira, M.V. de O. Cardoso, A.C.G. de Brito, L.M. Farias dos Santos, M.Z. Hernandes, A.C. Kiperstok, R.S. de Lima and M.B.P. Soares

Bioorg. Med. Chem. **14**, 3749-3757 (2006)

A novel series of thiosemicarbazone, aminoacyl-thiazolidone and their derivatives structures have anti-Trypanosoma cruzi activity. Biological evaluation showed that some of these compounds are able to inhibit the growth of T. cruzi in concentrations non-cytotoxic to mammalian cells. Docking studies are performed to investigate the binding pattern of these compounds for the T. cruzi cruzain (TCC) protein, have a significant correlation with experimental data.

Synthesis, antiviral activity, and pharmacokinetic evaluation of P3 pyridylmethyl analogs of oximinoarylsulfonyl HIV-1 protease inhibitors.

J.T. Randolph* [Abbott Labs], P.P. Huang, W.J. Flosi, David DeGoey, L.L. Klein, C.M. Yeung, C. Flentge, Mingua Sun, Chen Zhao, Tatyana Dekhtyar, Hongmei Mo, Lynn Colletti, Warren Kati, K.C. Marsh, A. Molla and D.J. Kempf

Bioorg. Med. Chem. **14**, 4035-4046 (2006)

Potent analogues of oximinoarylsulfonamides of HIV-1 aspartyl protease, provided low nanomolar EC_{50} values against both wild-type HIV and resistant mutant virus (A17). Pharmacokinetic results of these compounds showed good exposure when co-administered orally with an equal amount of ritonavir in the rat, with average AUC >8 μg h/mL. The 3-pyridylmethyl analog gave the best overall exposure, is the potent inhibitor of cytochrome P450 3A (K_i = 2.4 nM).

A density functional study of flavonoid compounds with anti-HIV activity.

J. Lameira, C.N. Alves* [Univ. of Federal do Para], V. Moliner and E. Silla

Euro.J. Med. Chem. **41**, 616-623 (2006)

DFT/B3LYP with the 6-31G* basis set is employed to calculate a set of molecular properties of 26 flavonoid compounds with anti-HIV activity. The multiple linear regression method is used to correlate the biological activity and structural properties. The anti-HIV activity of compounds are related with the molecular hydrophobicity, the electronegativity and the charges on some key atoms, while that the toxicity is related with the electronic affinities (EA), ClogP and charge on atom 8.

The influence of target family and functional activity on the physicochemical properties of pre-clinical compounds.

Richard Morphy* [Organon Labs]

J. Med. Chem., **49** (10), 2898 -2908 (2006)

The ligands for peptide GPCRs are found to be less efficient than the ligands for monoamine GPCRs. The changes in the property values during the optimization process are found to vary only across the target families, with the main determinant of the drug-likeness of the optimized compounds. Agonists for monoamine GPCRs, opioid receptors and ion channels are typically smaller and less lipophilic than the antagonists, but there is no difference between the agonists and the antagonists for peptide GPCRs and nuclear receptors.

Medicinal Chemistry and Drug Design (cont'd)

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.

Oren M. Becker* [Predix Pharm.], D.S. Dhanoa, Y. Marantz, Dongli Chen, Sharon Shacham, Srinivasa Cheruku, Alexander Heifetz, Pradyumna Mohanty, Merav Fichman, Anurag Sharadendu, Raphael Nudelman, Michael Kauffman, and Silvia Noiman

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

Discovery of a novel, potent, and selective amidosulfonamide nonazapirone 5-HT$_{1A}$ agonist for the treatment of anxiety and depression, for generalized anxiety disorder (GAD) is reported. PREDICT methodology is used to model the 3D structure of 5-HT$_{1A}$, and then performing in silico screening on that structure leading to the discovery of a 1 nM lead compound. The lead compound is optimized following a strategy devised based on in silico 3D models and realized through an in silico-driven optimization process, rapidly overcoming selectivity issues (affinity to 5-HT$_{1A}$ vs α1-adrenergic receptor) and potential cardiovascular issues (hERG binding), leading to a clinical compound.

A combination of molecular dynamics and docking calculations to explore the binding mode of ADS-J1, a polyanionic compound endowed with anti-HIV-1 activity.

Fabrizio Manetti, Cristina Tintori, M. Armand-Ugón, Imma Clotet-Codina, Silvio Massa, Rino Ragno, José A. Esté, and Maurizio Botta* [Univ. di Roma "La Sapienza]

J.Chem.Info. & Mod. **46**, 1344-1351 (2006)

Molecular modeling investigations on ADS-J1, a polyanionic compound with anti-HIV activity that is able to interfere with gp120-coreceptor interactions are presented. Computer simulations suggested that the V3 loop of gp120 is the preferential binding site for ADS-J1 onto HIV-1. Mutations induced by the inhibitor significantly changed the stereoelectronic properties of the gp120 surface, justifying a marked drop in the affinity of ADS-J1 toward an ADS-J1-resistant HIV-1 strain.

Immunophysical properties and prediction of activities for vaccinia virus complement control protein and smallpox inhibitor of complement enzymes using molecular dynamics and electrostatics.

Li Zhang, and Dimitrios Morikis* [Univ. of Calif.]

Biophys. J. **90**, 3106-3119 (2006)

MD simulations and Poisson-Boltzmann-type electrostatic calculations are used to the immunophysical modeling for VCP, SPICE, and three mutants. VCP and SPICE are homologous viral proteins that control the complement system by imitating, structurally and functionally, natural regulators of complement activation. The results are compared with experimental data to form correlations between the overall positive electrostatic potential of VCP/SPICE with binding and activity. These correlations are used to predict the binding and activity properties.

Stably tethered multifunctional structures of defined composition made by the dock and lock method for use in cancer targeting.

Edmund A. Rossi, David M. Goldenberg* [Immunomedics Inc.,] , Thomas M. Cardillo, William J. McBride, Robert M. Sharkey, and Chien-Hsing Chang

PNAS. **103,** 6829-6834 (2006)

Dock and lock method is described and applied to study the binding between the regulatory subunits of cAMP-dependent protein kinase and the anchoring domains of A kinase anchor proteins.   This approach allowed quantitative and site-specific coupling of many different biological substances for diverse medical applications. This method is validated by producing bispecific, trivalent-binding complexes composed of three stably linked Fab fragments capable of selective delivery of radiotracers to human cancer xenografts, resulting in rapid, significantly improved cancer targeting and imaging, providing tumor/blood ratios.

Medicinal Chemistry and Drug Design (cont'd)

Correlation weighting of valence shells in QSAR analysis of toxicity.

A.A. Toropov* [Inst. Res. Pharm.] and Emilio Benfenati

QSAR is proposed for predicting the toxicity LC_{50}-96h of 274 organic pesticides through optimizing of correlation weights of local and global graph invariants. The obtained best model used weighted $S2_k$ and global LHFG invariants.

Bioorg. Med. Chem. **14**, 3923-3926 (2006)

Quantitative Structure-Activity Relations

Comparative structure-activity relationships of benztropine analogues at the dopamine transporter and histamine H_1 receptors.

S.S. Kulkarni, T.A. Kopajtic, J.L. Katz and A. H. Newman* [Nat. Inst. on Drug Abuse, Baltimore]

Bioorg. Med. Chem. **14**, 3625-3634 (2006)

Benzotropine and its analogues showed higher binding affinities than the histamine H_1 receptor and DAT. Histamine H1-antagonist pharmacophore model is developed based on the cyproheptadine template, using a five-point superposition of classical antagonists. The molecular models at the DAT and histamine H1 receptor are providing further insight into the structural requirements for binding affinity and selectivity for further drug design.

A new type of ketolide bearing an *N*-aryl-alkyl acetamide moiety at the C-9 iminoether: Synthesis and structure-activity relationships (2).

Takashi Nomura* [Shionogi & Co.Ltd.], Tsutomu Iwaki, Yukitoshi Narukawa, Koichi Uotani, Toshihiko Hori, and Hideaki Miwa

Bioorg. Med. Chem. **14**, 3697-3711 (2006)

N-aryl-alkyl acetamide moiety at the C-9 iminoether and its analogues were examined for their antibacterial activities and pharmacokinetic properties. It was found that the introduction of an (*R*)-alkyl group between the amide and iminoether groups improved the pharmacokinetic properties. The compound with an *N*-(3-quinoxalin-6-yl-propyl)-propionamide moiety have in vivo efficacy comparable to CAM with potent in vitro antibacterial activities against the key respiratory pathogens including Haemophilus influenzae and erythromycin-resistant S. pneumoniae.

Synthesis and structure-activity relationships (SARs) of 1,5-diarylpyrazole cannabinoid type-1 (CB$_1$) receptor ligands for potential use in molecular imaging.

S.R. Donohue* [NIH], C. Halldin, and V.W. Pike

Bioorg. Med. Chem. **14**, 3712-3720 (2006)

SAR is examined on Cannabinoid type-1 (CB$_1$) receptor ligands, derived from the 1,5-diarylpyrazole template of rimonabant. The present study is focused on the potential discovery of CB1 receptor radioligands, which is used as probes with in vivo molecular imaging.

Quantitative Structure-Activity Relationships (cont'd)

β-Nitrostyrene derivatives as potential antibacterial agents: A structure-property-activity relationship study.

Nuno Milhazes, Rita Calheiros, M. Paula M. Marques, Jorge Garrido, M. Natália D.S. Cordeiro, Cátia Rodrigues, Sandra Quinteira, Carla Novais, Luísa Peixe and Fernanda Borges* [Univ. of Porto]

Bioorg. Med. Chem. **14**, 4078-4088 (2006)

Structural property-activity-relationship approach is applied through linear regression analysis to obtain a correlation between the physicochemical parameters of the compounds and their bacterial activity. The β-nitrostyrene compounds showed lower activity towards all the tested bacteria relative to the β-methyl-β-nitrostyrene analogues. The SPAR results are well agreed with the redox potentials and the antibacterial activity of the series of β-nitrostyrene derivatives.

In silico ADME modelling 2: Computational models to predict human serum albumin binding affinity using ant colony systems.

G.B. Sitarama, Ramamurthi Narayanan* [Tata Consultancy Serv. Ltd.], and Akash Khandelwal

Bioorg. Med. Chem. **14**, 4118-4129 (2006)

A stochastic method with multiple linear regressions is used to derive optimal QSPR models based on five and six descriptors with excellent predictive power. The best five-descriptor model is based on Kier and Hall valence connectivity index, Auto-correlation descriptor weighted by atomic masses, Auto-correlation descriptor weighted by atomic polarizabilities, AlogP98, SklogS. The results showed that the binding affinity of small organic compounds to human serum albumin is depending on the hydrophobic interactions, solubility, size and shape.

Linear and nonlinear QSAR study of *N*-hydroxy-2-[(phenylsulfonyl)amino]acetamide derivatives as matrix metalloproteinase inhibitors.

M. Fernández, Julio Caballero* [Univ. of Matanzas], and A. Tundidor-Camba.

Bioorg. Med. Chem. **14**, 4137-4150 (2006)

2D autocorrelation descriptors are used to model the inhibitory activity toward matrix metalloproteinases of *N*-hydroxy-2-[(phenylsulfonyl)amino]acetamide derivatives (HPSAAs). The relevant molecular descriptors are selected by linear and nonlinear genetic algorithm feature selection using multiple linear regression and Bayesian-regularized neural network approaches. The results are providing molecular information about the ligand specificity for MMP S_1', S_1, and S_2' pockets.

QSAR study of 1,4-dihydropyridine calcium channel antagonists based on gene expression programming.

Hong Zong Si* [Lanzhou Univ.], Tao Wang, Ke Jun Zhang, Zhi De Hu, and Bo Tao Fan

Bioorg. Med. Chem. **14**, 4834-4841 (2006)

The gene expression programming is used to develop quantitative model as a potential screening mechanism for a series of 1,4-dihydropyridine calcium channel antagonists. The heuristic method is used to search the descriptor space and select the descriptors responsible for activity. A nonlinear, six-descriptor model based on gene expression programming with mean-square errors 0.19 was set up with a predicted correlation coefficient (R^2) 0.92. This method provides a new and effective method for drug design and screening.

Synthesis, study of 3D structures, and pharmacological activities of lipophilic nitroimidazolyl-1,4-dihydropyridines as calcium channel antagonist.

Ramin Miri* [Shiraz Univ. of Med.Sci.], Katayoun Javidnia, Hasti Sarkarzadeh, and Bahram Hemmateenejad

Bioorg. Med. Chem. **14**, 4842-4849 (2006)

QSAR studies showed that the potency of nifedipine analogues was dependent upon lipophilicity, an electronic term and separated terms for each position on the DHP ring. The results for asymmetrical esters showed that lengthening of the substituent in C_3 ester substituent increased activity. When increasing of the length is accompanied by increasing the hindrance, the activity decreased. The results showed that all compounds were more active or similar in effect to that of the reference drug nifedipine.

Quantitative Structure-Activity Relationships (cont'd)

The application of a 3D-QSAR (*auto*MEP/PLS) approach as an efficient pharmacodynamic-driven filtering method for small-sized virtual library: Application to a lead optimization of a human A₃ adenosine receptor antagonist.

Stefano Moro* [Univ. di Padova], M. Bacilieri, B. Cacciari, C. Bolcato, C. Cusan, G. Pastorin, Karl-Norbert Klotz, and G. Spalluto

Bioorg. Med. Chem. **14**, 4923-4932 (2006)

3D-QSAR (*auto*MEP/PLS) method is applied with the combination of molecular electrostatic potential (MEP) surface properties (autocorrelation vectors) with the conventional partial least squares (PLS) analysis to predict the human A₃ receptor antagonist activities. A small-sized combinatorial library (841 compounds) is derived from the scaffold of the known human A₃ antagonist pyrazolo-triazolo-pyrimidines to prove this method as an efficient and alternative pharmacodynamic filtering for small-size virtual library.

QSAR modeling of the inhibition of Glycogen Synthase Kinase-3.

Alan R. Katritzky* [Univ. of Florida], Liliana M. Pacureanu, Dimitar A. Dobchev, Dan C. Fara, Pablo R. Duchowicz, and Mati Karelson

Bioorg. Med. Chem. **14**, 4987-5002 (2006)

CODESSA PRO is used to develop quantitative structure-activity relationship models of the biological activity of 277 inhibitors of Glycogen Synthase Kinase-3 using geometrical, topological, quantum mechanical, and electronic descriptors. The linear and nonlinear models obtained link the structures to their reported activity pIC_{50}. The main factors which are influencing the inhibitory activity of the GSK-3 enzyme are discussed.

New potent 5-nitrofuryl derivatives as inhibitors of *Trypanosoma cruzi* growth. 3D-QSAR (CoMFA) studies.

G. Aguirre, M. Boiani, E. Cabrera, Hugo Cerecetto* [Univ. de la Republica], R. Di Maio, M. González, A. Denicola, C. Mauricio R. Sant'Anna, and E.J. Barreiro

Euro.J. Med. Chem. **41**, 457-466 (2006)

Growth inhibitory activity in vitro of sixteen new 5-nitrofuryl derivatives against the protozoan parasite *Trypanosoma cruzi*, the causative agent of American trypanosomiasis, is studied. 3D-QSAR studies based on CoMFA are performed, the best model gave the importance of a specific hydrogen-bonding pattern around the carbonyl or thiocarbonyl moieties, as well as the requirement for hydrophobic lateral chains.

Non-stochastic quadratic fingerprints and LDA-based QSAR models in hit and lead generation through virtual screening: theoretical and experimental assessment of a promising method for the discovery of new antimalarial compounds.

A. Montero-Torres* [Cent. Univ. of Las Villas], R.N. García-Sánchez, Y. Marrero-Ponce, Y. Machado-Tugores, J.J. Nogal-Ruiz, A.R. Martínez-Fernández, V.J. Arán, Carmen Ochoa, A. Meneses-Marcel, and F. Torrens

Euro.J. Med. Chem. **41**, 483-493 (2006)

TOMOCOMD-CARDD is used to compare the quantitative models of the compounds, which are having antimalarial activity. The theoretical predictions are well agreed with the experimental results. The results are further useful in rational antimalarial-drug design and development.

Quantitative structure activity relationship of benzoxazinone derivatives as neuropeptide Y Y5 receptor antagonists

S. Deswal and N. Roy* [Nat. Inst. of Pharm. Edu. & Res.]

Euro.J. Med. Chem. **41**, 552-557 (2006)

QSAR studies are used with the genetic algorithm and multiple linear regression to generate the relationship between biological activity and calculated descriptors. The best model is developed using four descriptors from topological, thermodynamic, spatial and electrotopological class. The model is validated through cross validation, randomization and external test set prediction.

Quantitative Structure-Activity Relationships (cont'd)

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. Dyhring Jørgensen, Dan Peters, Tommy Liljefors, and Thomas Balle* [Danish Univ. of Pharm. Sci.]

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

The GRID/GOLPE approach is used to develop 3D-QSAR model, interpreted in terms of contour maps of the PLS coefficients and in terms of a homology model of the $\alpha_4\beta_2$ subtype of the nicotinic acetylcholine receptors. The hydrogen bonding from both hydrogens on the protonated amine and from the pyridine nitrogen to a water molecule as well as van der Waals interactions between the substituent bearing the protonated amine and the receptor is of importance for ligand affinity. 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.

Design, molecular modeling, synthesis, and anti-HIV-1 activity of new indolyl aryl sulfones: Novel derivatives of the indole-2-carboxamide.

Rino Ragno* [Univ. di Roma La Sapienza], A. Coluccia, G. La Regina, G. De Martino, F. Piscitelli, A. Lavecchia, E. Novellino, A. Bergamini, C. Ciaprini, A. Sinistro, G. Maga, E. Crespan, M. Artico, and R. Silvestri.

J. Med. Chem., **49** (10), 3172 -3184 (2006)

Molecular modeling studies and highly predictive 3-D QSAR model led to the discovery of exceptionally potent indolyl aryl sulfones (IASs) characterized by the presence of either a pyrrolidyn-2-one nucleus at the indole-2-carboxamide or some substituents at the indole-2-carbohydrazide. It is observed that two compounds are active in the sub-nanomolar range of concentration in both MT-4 and C8166 cell-based anti-HIV assays. These compounds showed excellent inhibitory activity against both HIV-112 and HIV-AB1 primary isolates in lymphocytes and against HIV WT in macrophages.

Quantitative structure-activity relationship studies on inhibition of HERG potassium channels.

K. Yoshida and Tomoko Niwa* [Nippon Shinyaku Co., Ltd.]

J.Chem.Info. & Mod. **46,** 1371-1378 (2006)

2D-QSAR studies are performed on 104 HERG channel blockers with diverse structures and formulated interpretable models to guide chemical-modification studies and virtual screening. Statistically significant descriptors are selected by a genetic algorithm, and the final model included the octanol/water partition coefficient, topological polar surface area, diameter, summed surface area of atoms. The correspondence of the molecular determinants derived from the 2D-QSAR models with the 3D structural characteristics of the putative binding site in a homology-modeled HERG channel is discussed.

A genetic-function-approximation-based QSAR model for the affinity of arylpiperazines toward α_1 adrenoceptors.

L. Maccari, M. Magnani, G. Strappaghetti, F. Corelli, Maurizio Botta* [Univ. di Perugia] and F. Manetti

J.Chem.Info. & Mod. **46***,* 1466-1478 (2006)

The genetic function approximation algorithm is used to generate a QSAR equation to correlate the structural properties of arylpiperazine derivatives with their affinity toward the α_1 adrenoceptor (α_1-AR). The new model is compared with the previous pharmacophore for α_1-AR antagonists and a QSAR model for α_2-AR antagonists with the aim of finding common or different key determinants influencing both affinity and selectivity toward α_1- and α_2-AR.

Quantitative Structure-Activity Relationships (cont'd)

Diagnostic tools to determine the quality of "Transparent" regression-based QSARs: The "Modelling Power" plot.

Salvador Sagrado* [Univ. de Valencia], and M.T. D. Cronin

J.Chem.Info. & Mod. **46**, 1523-1532 (2006)

A bivariate plot is presented for comparing two or more QSAR models based on descriptive power (Dp) and predictive power (Pp), two new regression models. Descriptive power is estimated through the relative uncertainty of model coefficients, and the predictive power is estimated through both the fitted and cross-validated explained variance of the response variable. The results are intuitive impression of the descriptive, global importance of the selected descriptors and predictive (possibility of performing QSAR and SAR estimations) power.

Host-Guest Systems

Evolution of the Thienopyridine Class of Inhibitors of IκB Kinase-β: Part I: Hit-to-Lead Strategies.

Tina Morwick* [Boehringer Ingelheim Pharm.], A. Berry, J. Brickwood, M. Cardozo, K. Catron, M. DeTuri, J. Emeigh, C. Homon, M. Hrapchak, S. Jacober, S. Jakes, P. Kaplita, T.A. Kelly, J. Ksiazek, M. Liuzzi, R. Magolda, Can Mao, D. Marshall, D. McNeil, A. Prokopowicz, III, C. Sarko, E. Scouten, C. Sledziona, S. Sun, J. Watrous, J. Ping Wu, and C. L. Cywin

J. Med. Chem. **49**, 2898 -2908 (2006)

High-throughput screening is used to describe in detail for a collection of screening hits identified as inhibitors of IκB kinase- β (IKK β). A promising hit series is selected and subsequent lead generation activities included the development of a pharmacophore hypothesis and structure-activity relationship for the hit series from the results. This led to the exploration of related scaffolds offering additional opportunities, and the various structural classes were comparatively evaluated for enzyme inhibition, selectivity, and drug-like properties. A novel lead series of thienopyridines is established, and this series advanced into lead optimization for further development.

2D Structure depiction.

A.M. Clark* [Chem. Comp. Group Inc.], P. Labute, and M. Santavy.

J.Chem.Info. & Mod. **46**, 1107-1123 (2006)

An algorithm to depict 2d coordinates of chemical structures is described in detail and measurements of its overall success are presented.

A!
Pharmacophore modeling and in silico screening for new P450 19 (Aromatase) inhibitors.

D. Schuster, C. Laggner, T.M. Steindl, A. Palusczak, R.W. Hartmann, and Thierry Langer* [Saarland Univ.]

J.Chem.Info. & Mod. **46**, 1301-1311 (2006)

The present study analyzes chemical features common to P450 19 inhibitors to develop ligand-based, selective pharmacophore models for this enzyme. The HipHop and HypoRefine algorithms implemented in the Catalyst package are used to create both common feature and quantitative models. The common feature model for P450 19 includes two ring aromatic features in its core and two hydrogen bond acceptors at the ends. The models are used as database search queries to identify active compounds from the NCI database.

Host-Guest Systems (cont'd)

A!
Influence of the conditions in pharmacophore generation, scoring, and 3D-database search for chemical feature-based pharmacophore models: One application study of ET_A- and ET_B-selective antagonists.

J.R. Cucarull-Gonzàlez* [Univ. Autonoma de Barcelona],
C. Laggner, and T. Langer

Catalyst is used to study the influence of the compare scaled MultiBlob feature errors. The influence of this parameter is studied in pharmacophore generation, hypothesis scoring, and database searching. Two different pharmacophore models are constructed for the ET_A and ET_B receptor antagonists. Both models are compared, and some differences in the position of the hydrogen-bond acceptor in the putative binding pocket is highlighted.

Carbon Nanoparticles

Dendrimer-templated Fe nanoparticles for the growth of single-wall carbon nanotubes by plasma-enhanced CVD.

P. B. Amama* [Purdue Univ.], M.R. Maschmann,
T. S. Fisher, and T. D. Sands

A fourth-generation (G4) poly(amidoamine) (PAMAM) dendrimer (G4-NH_2) is used as a template to deliver monodispersed catalyst nanoparticles to SiO_2/Si, Ti/Si, sapphire, and porous anodic alumina (PAA) substrates. The results are used to expose Fe nanoparticles supported on different substrates for the growth of high-quality SWNTs by PECVD.

Polymer-Functionalized multiwalled carbon nanotubes as lithium intercalation hosts.

X. Wang, Hewen Liu* [Univ. of Sci. & Tech. of China],
Yi Jin, and Chunhua Chen

The multiwalled carbon nanotubes (MWNT) functionalized with linear poly(ethylene glycol) showed a high initial capacity of lithium insertion/deinsertion but had the highest capacity fade rate among the materials. The polymers are chemically localized in the electrode-electrolyte interface, the comparison between hyperbranched and linear polymer-modified MWNTs manifested the important influence of the electrode-electrolyte interface on the electrochemical properties of lithium batteries.

Chemical functionalization of carbon nanotubes by carboxyl groups on stone-wales defects: A density functional theory study.

Chenchen Wang, Gang Zhou, Haitao Liu, Jian Wu, Yong Qiu, Bing-Lin Gu, and Wenhui Duan* [Tsinghua Univ.]

DFT theory is used to investigate the chemical functionalization of carbon nanotubes with Stone-Wales (SW) defects by carboxyl (COOH) groups. It was found that the double-adsorption system is more energetically favorable than the monoadsorption one. The adsorption of COOH groups leads to a significant change of the electronic states around the Fermi level, which is advantageous for the electrical conductivity.

Liquid Crystals

Orientation dynamics in isotropic phases of model oligofluorenes: Glass or liquid crystal.

E. Somma* [Univ. of Crete]

MD simulations are used to investigate defect-free oligofluorenes. This is well accounted for by the Landau-de Gennes theory, with a strong temperature dependence of the viscosity coefficient, reflecting the proximity of the glass transition. For the trimer the two transitions almost overlap and the molecular orientation coincide with the α-relaxation associated with the glass transition.

| 1.2. | *Biopolymers* |

Bioinformatics

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

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

J. Chem. Theory. & Comp. **2**, 840 -857 (2006)

In this, how the computation of a transition network is achieved for a complex protein transition. An efficient hierarchical procedure is used to uniformly sample the conformational subspace relevant to the transition. Then, the best path which connects the end states is determined as well as the rate-limiting ridge on the energy surface which separates them. This approach is used for the conformational switch of Rasp21.

Dramatic performance enhancements for the FASTER optimization algorithm.

Benjamin D. Allen, Stephen L. Mayo* [California Inst. of Tech.]

J.Comp. Chem. **27,** 1071-1075 (2006)

FASTER is used to calculate low-energy side-chain configurations in side-chain placement and protein design. The results showed that the efficiency is improved by stringently limiting the number of positions that are allowed to relax in response to a perturbation. The improved FASTER algorithm finds low-energy solutions more efficiently than common optimization schemes. These advances have prompted investigations into new methods for force field parameterization and multiple state design.

Definition of systematic, approximately separable, and modular internal coordinates (SASMIC) for macromolecular simulation.

P. Echenique* [Univ. de Zaragoza], and J. L. Alonso

J.Comp. Chem. **27,** 1076-1087 (2006)

SASMIC are written in Z-matrix form and is directly implemented using only topological information. *Ab initio* quantum mechanical calculations are used to assess the commonly assumed approximation of the free energy, obtained from "integrating out" the side chain degree of freedom, by the potential energy surface in the protected dipeptide HCO-**L**-Ala-NH$_2$. A subbox of the Hessian matrix in two different sets of coordinates to illustrate the approximate separation of soft and hard movements when the coordinates defined in this work are used.

Protein Structure Prediction

Stochastic kinetics of viral capsid assembly based on detailed protein structures.

M. Hemberg, S.N. Yaliraki, and M. Barahona* [Imperial Coll.]

Biophys. J. **90**, 3029-3042 (2006)

A generic computational framework for the simulation of viral capsid assembly is presented. It showed that how the quasi-stationary kinetics of assembly is described as a Markovian cascading process, in which only a few intermediates and a small proportion of pathways are present. The observed pathways and intermediates can be related a posteriori to structural and energetic properties of the capsid oligomers.

Structural instability of the prion protein upon M205S/R mutations revealed by molecular dynamics simulations.

T. Hirschberger, M. Stork, B. Schropp, K.F. Winklhofer, J. Tatzelt and P. Tavan* [Ludwig-Maximilians-Univ.]

Biophys. J. **90**, 3908-3918 (2006)

The native PrP^C structure becomes strongly distorted within a few nanoseconds, once the point mutations M205S and M205R. In M205R, distortion is characterized by a motion of helix 1 away from the hydrophobic core into the aqueous environment and a subsequent structural decay. This decay suggested that the hydrophobic attachment of helix 1 to helix 3 at M205 is required for its correct folding into its stable native structure.

Comparative or Homology Modeling

Elucidation of sulfadoxine resistance with structural models of the bifunctional *Plasmodium falciparum* dihydropterin pyrophosphokinase-dihydropteroate synthase.

Tjaart A.P. de Beer, Abraham I. Louw* [Univ. of Pretoria], and Fourie Joubert

Bioorg. Med. Chem. **14**, 4433-4443 (2006)

Saccharomyces cerevisiae, Mycobacterium tuberculosis, Bacillus anthracis, and Escherichia coli crystal structures are used as templates to construct the homology models of the bifunctional *P. falciparum* dihydropterin pyrophosphokinase–dihydropteroate synthase enzyme. MD simulations are used to solvate and to refine the resulting structures. Sulfadoxine is superimposed into the equivalent position of the *p*-aminobenzoic acid substrate and its binding parameters are refined using minimization and molecular dynamics.

Interaction of novel condensed triazine derivatives with central and peripheral type benzodiazepine receptors: synthesis, in vitro pharmacology and modeling.

Éva Szárics, Zsuzsanna Riedl, Lajos Nyikos, György Hajós, and Julianna Kardo* [Hungarian Academy of Sci.]

Euro.J. Med. Chem. **41**, 445-456 (2006)

Molecular interactions between selected ligands and $\alpha_1\gamma_2$ subunit-interface residues in a GABA$_A$ receptor extracellular domain homology model is calculated. The resulting data is compared with calculations confirmed hydrogen bonding to γ_2Thr142 and hydrophobic interaction with α_1His101 is essential for high-affinity CBR binding.

Construction of human ghrelin receptor (hGHS-R1a) model using a fragmental prediction approach and validation through docking analysis.

Alessandro Pedretti, Marco Villa, Marco Pallavicini, Ermanno Valoti, and Giulio Vistoli* [Univ. di Milano]

J. Med. Chem. **49** (10), 3077 -3085 (2006)

The fragmental approach is used to build the human ghrelin receptor (hGHS-R1a) model and is examined by docking the tetrapeptide Gly-Ser-Ser(*n*-octanoyl)-Phe-NH$_2$. Docking results confirmed the relevance of two distinct subpockets: a polar cavity bearing the key residues involved in receptor activation and an aromatic/apolar subpocket, plays an important role in determining the high constitutive activity of hGHS-R1a. The docking scores of both subpockets are in remarkable agreement with biological data, emphasizing that the model is used to predict the activity of novel ligands. The results highlight the potential of the fragmental approach to build improved models for any GPCR.

Homology modeling of human serum carnosinase, a potential medicinal target, and MD simulations of its allosteric activation by citrate.

Giulio Vistoli* [Univ. di Milano], Alessandro Pedretti, Matteo Cattaneo, Giancarlo Aldini, and Bernard Testa

J. Med. Chem. **49** (10), 3269 -3277 (2006)

Homology modeling is used to built the human serum carnosinase enzyme on the basis of β-alanine synthetase, and its active center to bind known substrates carnosine, homocarnosine, and anserine in a binding mode conducive to catalysis. Citrate ions are binding at only three well-defined sites involving both ion pairs and hydrogen bonds. MD simulations proved that citrate binding had a remarkable conformational influence on the 3D structure of carnosinase, increasing the binding affinity of carnosine to the catalytic site.

Structural analysis of an Echinococcus granulosus actin-fragmenting protein by small-angle X-Ray scattering studies and molecular modeling.

E.D. Grimm, R.V. Portugal, Mário de Oliveira Neto, N.H. Martins, I. Polikarpov, A. Zaha, and H.B. Ferreira* [Centro de Biotech.]

Biophys. J. **90**, 3216-3223 (2006)

Two different molecular homology models are built for EgAFFP, but only one was validated through SAXS studies. The predicted structure for EgAFFP consists of three repeats of a central *β*-sheet sandwiched between one short and one long α-helix, possible implications of the structure of EgAFFP upon actin binding are discussed.

Comparative or Homology modeling (cont'd.)

Comparative protein modeling of 1-deoxy-D-xylulose-5-phosphate reductoisomerase enzyme from Plasmodium falciparum: A potential target for antimalarial drug discovery.

Nidhi Singh, Gwenael Cheve, Mitchel A.Avery, and Christopher R.McCurdy*[Univ. of Mississippi]

J.Chem.Info. & Mod. **46**, 1360-1370 (2006)

Comparative modeling is used to construct the three-dimensional model of this enzyme through multiple alignment followed by intensive optimization, minimization, and validation. The resulting model demonstrates a reasonable topology as gauged from the Ramachandran plot and acceptable three-dimensional structure compatibility as assessed by the Profiles-3D score. A set of known inhibitors of DXR were also docked into the active site of the modeled Pf-DXR. The docked scores correlated well with experimental pIC_{50} values. The results are useful in the early design and development of inhibitors by either de novo drug design or virtual screening of large small-molecule databases leading to development of new antimalarial agents.

Protein Folding

Folding, misfolding, and amyloid protofibril formation of WW Domain FBP28.

Yuguang Mu* [Nanyang Tech.Univ.], Lars Nordenskiöld, and James P. Tam

Biophys. J. **90**, 3983-3992 (2006)

MD simulations are used with explicit water model to study the folding mechanism of a triple β-strand WW domain from the Formin binding protein 28 (FBP28). In the free energy landscape a transition state is identified and its structures and ø-values are compared with experimental data from a homologous protein, the prolyl-isomerase Pin1 WW domain. The aggregation behavior of the FBP28 WW domain is related to one such misfolded structure, which has a much lower free energy of dimer formation than that of the native dimer.

Protein Design and Engineering

A designed glycoprotein analogue of Gc-MAF exhibits native-like phagocytic activity.

Federica Bogani, Elizabeth McConnell, Lokesh Joshi, Yung Chang, and Giovanna Ghirlanda* [Arizona State Univ.]

J. Am. Chem. Soc. **128**, 7142 -7143 (2006)

De novo protein engineering is used to develop a mini-protein analogue of Gc-MAF, a glycoprotein involved in the immune system activation that showed anticancer activity in mice. Molecular modeling tools are used in conjunction with structural analysis to splice the glycosylated loop onto a stable three-helix bundle. The resulting 69-residue model peptide, MM1, is synthesized by solid-phase synthesis both in the aglycosylated and the glycosylated (GalNAc-MM1) form. GalNAc-MM1 provides a framework for the development of mutants with increased activity that is used in place of Gc-MAF as an immunomodulatory agent in therapy.

A designed branched three-helix bundle protein dimer.

Gunnar T. Dolphin* [Linköping Univ.]

J. Am. Chem. Soc. **128**, 7287 -7290 (2006)

The design and synthesis of a uniquely branched three-helix bundle that folds into a well-folded dimeric protein is presented. The branching of this protein is performed by the native chemical ligation method, provides a chemoselective and stable amide bond between the unprotected fragments. The results showed that the folded protein is present as a stable and highly helical dimmer, which is forming a six-helix bundle.

Protein Dynamics

Structural and dynamical properties of a full-length HIV-1 integrase: Molecular dynamics simulations.

A. Wijitkosoom, S. Tonmunphean, T.N. Truong* [Univ. of Utah], and S. Hannongbua

J.Biomol. Stru. & Dynamics. **23,** 613-624 (2006)

MD simulations are used to investigate the structural and dynamical properties of the complete full-length structure of HIV-1 integrase. Simulations are applied on core domain, full-length structure without and with a Mg2+ in its active site to investigate the difference in the molecular properties of the full-length models.   The relative topology formed by an angle between the three domains, the cavity size defined by the catalytic triad, Asp64, Asp116, and Glu152, distances and solvation of the Mg2+, and conformation of the catalytic residues properties are observed.

Investigation of interaction between enolase and phosphoglycerate mutase using molecular dynamics simulation.

D. Hakobyan, and K. Nazaryan* [Nati. Acad. of Sci. of Armenia]

J.Biomol. Stru. & Dynamics. **23,** 625-634 (2006)

MD simulations are used to identify the complex formation between active centres of phosphoglycerate mutase (PGM) and enolase from Saccharomyces cerevisiae. PGM and enolase showed the binding affinity between their active regions and suggested that the substrate direct transfer mechanism is existed between enzymes.

Root mean square deviation probability analysis of molecular dynamics trajectories on DNA.

S.B. Dixit, S.Y. Ponomarev, and D.L. Beveridge* [Wesleyan Univ.]

J.Chem.Info. & Mod. **46,** 1084-1093 (2006)

Molecular simulations are used to study the differences and commonalities in multiple structural ensembles is an important step and for further insight into the conformation and dynamics of complex biomacromolecules. Probability analysis procedure based on the root-mean-square differences among the structural ensembles that efficiently and accurately performs the relevant comparison.

A protein dynamics study of photosystem II: The effects of protein conformation on reaction center function.

Sergej Vasil'ev* [Brock Univ.] and Doug Bruce

Biophys. J. **90**, 3062-3073 (2006)

MD simulations are used to investigate the structure and function of photosystem II. The results showed that the primary and secondary quinone electron acceptors, Q_A and Q_B, exhibited independent changes in position over the duration of the simulation. Q_B fluctuated between two binding sites similar to the proximal and distal sites previously observed in light- and dark-adapted RC from purple bacteria.

A molecular dynamics study of the effect of Ca^{2+} removal on calmodulin structure.

E. Project, R. Friedman, E. Nachliel, and Menachem Gutman* [Tel Aviv Univ.]

Biophys. J. **90**, 3842-3850 (2006)

MD simulations are used to study structural stability of the protein when one of its four bound Ca^{2+} ions is removed, and compared it to a simulation of the fully Ca^{2+} bound protein. It is found that the removal of a single Ca^{2+} ion from the N-lobe of the protein, which has a lower affinity for the ion, is sufficient to initiate a considerable structural rearrangement.

Free Energy

Free energy simulations of uncatalyzed DNA replication fidelity: Structure and stability of T·G and dTTP·G terminal DNA mismatches flanked by a single dangling nucleotide.

Urban Bren, Václav Martínek, and Jan Florián* [Loyola Univ. Chicago]

J. Phys. Chem. B. **110**, 10557 -10566 (2006)

FEP and linear interaction energy methods are used to study the DNA replication system included a hydrated duplex DNA with the 5'-CG dangling end of the templating strand. Binding-relevant free energy approach is characterized by its unique perturbation pathway and by its exclusion of the intramolecular energy of a rigid part of the ligand from the total potential energy.

Free volume hypothetical scanning molecular dynamics method for the absolute free energy of liquids.

Ronald P. White* [Univ. of Pittsburgh], and H. Meirovitch

J. Chem.Phys. **124**, 204108 -204121 (2006)

Recent version of the hypothetical scanning method called HSMC-EV, each TP is calculated from MC simulations. In this work, excluded volume (EV) is replaced by free volume (FV) approach. The development of the HSMD method for liquids is an advanced HS methodology. The results of the HSMD-FV approach are well agreed with the HSMC and thermodynamic integration results and the efficiency is equal to HSMC-EV.

Can free energy calculations be fast and accurate at the same time? Binding of low-affinity, non-peptide inhibitors to the SH2 domain of the src protein.

Christophe Chipot* [Univ. Henri Poincare], Xavier Rozanska, and Surjit B. Dixit

J.Comp.Aided Mol. Design. **19**, 765-770 (2006)

Free energy calculations are used for non-peptide inhibitors to the SH2 domain of the pp60 src tyrosine kinase. The sampling of the configurational space is necessary to minimize the statistical error and the sensitivity of binding free-energies to the parameters utilized imposes an appropriate parameterization of the potential energy function are provided. The obtained results gave an accurate ranking for four non-peptide mimes of a sequence recognized by the [pp60]src SH2 domain.

Energetics of ion permeation, rejection, binding, and block in gramicidin A from free energy simulations.

Turgut Basug, and Serdar Kuyucak* [Univ. of Sydney]

Biophys. J. **90**, 3941-3950 (2006)

A comprehensive test is considered the energetics of permeation for all three types of ions. The potential of mean force for K^+, Cl^-, and Ca^{2+} ions along the channel axis is constructed. For an independent check of the potential-of-mean-force results, the free energy differences for these ions at the channel center and binding sites relative to bulk are calculated and found that rejection of anions is satisfied.

Membrane Proteins and Lipid-Peptide Interactions

Supported lipopolymer membranes as nanoscale filters: Simultaneous protein recognition and size-selection assays.

Fernando Albertorio, Susan Daniel, and P.S. Cremer* [Texas A&M Univ.]

J. Am. Chem. Soc. **128**, 7168 -7169 (2006)

A new method is developed for size-selective discrimination of protein analytes by incorporating poly(ethylene glycol) lipopolymers into supported lipid bilayers. The membranes contained biotinylated lipids, which recognized both streptavidin and anti-biotin IgG. It is observed that on-chip ligand-receptor binding assay that favored streptavidin binding over anti-biotin by several orders of magnitude in the presence of the lipopolymer.

Ligand Binding

High-Throughput calculation of protein-ligand binding affinities: Modification and adaptation of the MM-PBSA protocol to enterprise grid computing.

S.P. Brown* [Abbott Labs.], and S.W. Muchmore.

J.Chem.Info. & Mod. **46,** 999-1005 (2006)

Molecular Mechanics with Poisson-Boltzmann Surface Area (MM-PBSA) methodologyis modified and combined with a coarse-grain parallelized implementation suitable for deployment onto this enterprise grid. It is possible to produce rapid physics-based estimates of protein-ligand binding affinities that are correlated with the experimental data and also comparing the correlation obtained from the binding-affinity calculations using traditional MM-PBSA that are reported.

Baicalein is a potent in vitro inhibitor against both reticulocyte 15-human and platelet 12-human lipoxygenases.

J.D. Deschamps, V.A. Kenyon, and Theodore R. Holman* [Univ. of California]

Bioorg. Med. Chem. **14**, 4295-4301 (2006)

The mechanism of baicalein inhibition of 15-hLO-1 is reductive, which molecular modeling suggested through direct binding of the catecholic moiety of baicalein to the iron. A structurally related flavonoid, apigenin, is not reductive, however, molecular modeling suggested a hydrogen bond with Thr591 may account for its inhibitor potency.

Hierarchical PLS modeling for predicting the binding of a comprehensive set of structurally diverse protein-ligand complexes.

A. Lindström, F. Pettersson, F. Almqvist, A. Berglund, J. Kihlberg, and Anna Linusson* [Umeå Univ.]

J.Chem.Info. & Mod. **46,** 1154-1167 (2006)

A new approach is presented, and models are developed based on the iformation available from the PDB bind database containing high-resolutin X-ray structures. The models are validated with an external set of 174 complexes from the 2003 release of the PDB bind database. The results showed that Hi-PLS methodology could facilitate the difficult task of predicting binding affinity.

A QXP-based multistep docking procedure for accurate prediction of protein-ligand complexes.

Laleh Alisaraie, Lars A. Haller, and Gregor Fels* [Univ. of Paderborn]

J.Chem.Info. & Mod. **46**, 1174-1187 (2006)

QXP-Flo+0802, molecular docking program is developed particularly for ligands with a high degree of rotational freedom that allows the accurate prediction of the orientation and conformation of ligands in protein binding sites. This is achieved by performing a series of successive multistep docking runs using a local Monte Carlo search with a restricted rotational angle, by which the conformational search space is limited.

Protein grabs a ligand by extending anchor residues: Molecular simulation for Ca^{2+} binding to calmodulin loop.

Chigusa Kobayashi, and Shoji Takada*[Kobe Univ.]

Biophys. J. **90**, 3043-3051 (2006)

The free-energy landscape between binding and conformational change is analyzed by using the AMBER force field with explicit water solvent, conducting umbrella sampling for the free-energy surface and steered molecular dynamics for the pathway search for Ca^{2+} binding to a calmodulin loop. It is found that, at an early stage of binding, some key residue side chains extend their "arms" to catch Ca^{2+} and, after catching, they carry the Ca^{2+} to the center of the binding pocket. This grabbing motion resulted in smooth and stepwise exchange in coordination partners of Ca^{2+} from water oxygen to atoms in the calmodulin loop.

Ligand Binding (cont'd)

Gated binding of ligands to HIV-1 protease: Brownian dynamics simulations in a coarse-grained model.

Chia-En Chang* [Univ. of Calif.], T. Shen, J. Trylska, V. Tozzini, and J.A. McCammon

Biophys. J. **90**, 3880-3885 (2006)

Brownian dynamics simulations are applied in a coarse-grained model to study the gated association rate constants of HIV-1 proteases and drugs. The simulations suggested that the flap flexibility and the opening frequency of the wild-type, the G48V and L90M mutants are similar, but the flaps of the variant G48V/V82A/I84V/L90M open less frequently, resulting in a lower gated rate constant. The developed methodology is fast and provides an efficient way to predict the gated association rate constants for various protease mutants and ligands.

Binding of 5'-GTP to the C-terminal FeS cluster of the radical *S*-adenosylmethionine enzyme MoaA provides insights into its mechanism.

Petra Hänzelmann, and Hermann Schindelin* [Stony Brook Univ.]

PNAS. **103,** 6829-6834 (2006)

The crystal structure of MoaA in complex with 5'-GTP provides valuable insights into the subsequent radical reaction. MoaA binds 5'-GTP with high affinity and interacts through its C-terminal [4Fe–4S] cluster with the guanine N1 and N2 atoms, in a yet uncharacterized binding mode. This structure visualizes the L-Met and 5'-dA cleavage products of SAM. Rotation of the 5'-dA ribose and/or conformational changes of the guanosine are proposed to bring the 5'-deoxyadenosyl radical into close proximity of either the ribose C2' and C3' or the guanine C8 carbon atoms leading to hydrogen abstraction.

Protein-Protein Interactions

A! & T!

Computer-aided analysis of the interactions of glutamine synthetase with its inhibitors.

Łukasz Berlicki* [Wroclaw U. of Tech.], and Paweł Kafarski

Bioorg. Med. Chem. **14**, 4578-4585 (2006)

Molecular modeling methods are used to study the inhibition mechanism of glutamine synthetase by phosphinothricin and its analogues. All the inhibitor-enzyme complexes are evaluated quantitatively by using eight scoring functions by implementing Insight and Sybyl program packages. It is observed that significant correlation is obtained between the scores and experimental pKi values. Computed surface charge distribution for five selected inhibitors in both free and phosphorylated forms and their comparison with electronic structure of enzymatic reaction transition state allowed to determine important electronic features required to construct potent inhibitors of glutamine synthetase.

Unraveling the importance of protein-protein interaction: Application of a computational alanine-scanning mutagenesis to the study of the IgG1 streptococcal protein G (C2 Fragment) complex.

I.S. Moreira, P.A. Fernandes, and M.J. Ramos* [Univ. of Porto]

J. Phys. Chem. B. **110**, 10962 -10969 (2006)

MM-PBSA approach, combined MM and continuum solvent are used to calculate the free energy differences through alanine mutation. New residues that are characterized as warm spots and, are important for complex formation. By increasing the functionality of this improved computational alanine-scanning mutagenesis approach testing its sensitivity to a protein-protein complex with an interface made up of residues mainly polar.

1.3.   Surfaces, Catalysts, and Material Subjects

The hidden role of acetate in the PbSe nanocrystal synthesis.

Arjan J. Houtepen* [Univ. Utrecht], Rolf Koole, Daniël Vanmaekelbergh, Johannes Meeldijk, and Stephen G. Hickey

J. Am. Chem. Soc. **128**, 6792 -6793 (2006)

The shape and size of the colloidal PbSe nanocrystals are determined by the concentration of acetate and that only acetate-free reaction mixtures result in spherical nanocrystals. The presence of acetate leads to efficient oriented attachment of smaller PbSe nanoparticles along the <100> crystal axis. The acetate is responsible for many of the PbSe crystal shapes and is possible to synthesize these star-shaped nanocrystals so monodisperse that they form ordered monolayers with crystal alignment.

Quantitative structure-activity relationships of ruthenium catalysts for olefin metathesis.

Giovanni Occhipinti, Hans-René Bjørsvik, and V.R. Jensen* [Univ. of Bergen]

*J. Am. Chem. Soc.***128**, 6952 -6964 (2006)

DFT theory is used to derive a QSAR model, both the independent and dependent variables are derived on a large set of 14-electron complexes, $LCl_2Ru=CH_2$, with different dative ligands. The multivariate model is correlated with the properties of the 14-electron complexes and the activity for the Grubbs ruthenium catalysts for olefin metathesis. The results promise for broader screenings of olefin metathesis catalysts as well as for development of homogeneous transition metal catalysts.

Generating suspended single-walled carbon nanotubes across a large surface area via patterning self-assembled catalyst-containing block copolymer thin films.

Jennifer Lu, Thomas Kopley, Dave Dutton, Jie Liu, Cheng Qian, Hyungbin Son, Mildred Dresselhaus, and Jing Kong* [Massachusetts Inst. of Tech.]

J. Phys. Chem. B. **110**, 10585 -10589 (2006)

Catalytically active nanostructures with controlled size and space are produced using self-assembled block copolymers as templates. A self-assembled polystyrene-*b*-polyferrocenylsilane thin film and monolayer of surface micelles of cobalt-complexed polystyrene-*b*-poly(2-vinylpyridine) are compatible with novolac-based conventional photoresists.

A methodology for investigating new nonprecious metal catalysts for PEM fuel cells.

D. Susac, A. Sode, L. Zhu, P. C. Wong, M. Teo, D. Bizzotto, K. A. R. Mitchell, R. R. Parsons, and S. A. Campbell* [Ballard Power Systems Inc.]

J. Phys. Chem. B. **110**, 10762 -10770 (2006)

A new method is used to investigate metal-chalcogen materials as catalysts for the oxygen reduction reaction in proton exchange membrane (PEM) fuel cells. The Co-Se thin films with varying Se are active for oxygen reduction, although the open circuit potential (OCP) is lower than for Pt.

Energy density analysis of cluster size dependence of surface-molecule interactions (II): Formate adsorption onto a Cu(111) surface.

Hiromi Nakai* [Waseda Univ.]

J.Comp. Chem. **27,** 917-925 (2006)

EDA is applied to examine surface-molecular interactions for different cluster sizes. The largest model cluster Cu_{56} showed that the adsorption-induced energy density variation in Cu atoms decays with distance from the adsorption site. This technique verified the reliability of the used model cluster and found that at least a four-layer model cluster is necessary to treat the surface-molecule interaction with chemical accuracy.

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2.   <u>METHODOLOGY</u>

Quantitative Structure-Activity Relations

Novel approach to evolutionary neural network based descriptor selection and QSAR model development.

Željko Debeljak* [Osijek Clinical Hospital], V. Marohnić, Goran Srečnik and M. Medić-Šarić

*J.Comp.Aided Mol. Design.***19,** 835-855 (2006)

Evolutionary neural network based QSAR approach is applied to examine the descriptor selection process towards stable descriptor subset (DS) composition characterized by acceptable generalization, as well as the influence of description stability on QSAR model interpretation. The principles of this method is applied and proposed a QSAR model for benzodiazepine and evaluated against the reported results in terms of final DS composition and model predictive performance.

Combinatorial QSAR modeling of P-Glycoprotein substrates.

Patricia de Cerqueira Lima, Alexander Golbraikh, Scott Oloff, Yunde Xiao, and Alexander Tropsha* [Targacept Inc.,]

J.Chem.Info. & Mod. **46,** 1245-1254 (2006)

QSAR/QSPR models are generated with a single modeling technique using one type of molecular descriptors. A combinatorial approach is applied to a data set of 195 diverse substrates and nonsubstrates of P-glycoprotein that has an important role in drug resistance. 16 combinations of techniques and descriptor types are considered for every QSAR modeling type. The combinatorial QSAR approach identified models with higher predictive accuracy than the previously reported for the same data set. In the absence of any universally applicable "one-for-all" QSAR methodology, the combinatorial QSAR approach should become the standard practice in QSPR/QSAR modeling.

3-D QSAR studies on histone deacetylase inhibitors: A GOLPE/GRID approach on different series of compounds.

Rino Ragno, Silvia Simeoni, Sergio Valente, Silvio Massa, and Antonello Mai* [Univ. degli Studi di Siena]

J.Chem.Info. & Mod. **46,** 1420-1430 (2006)

Docking simulations and 3D-QSAR studies are carried out with GRID/GOLPE combination on four series of HDAC inhibitors. The results are validated each other and provided insight into the structural requirements for anti-HDAC activity. This is the first 3-D QSAR application on a broad molecular diversity training set of HDACIs.

Development of a chirality-sensitive flexibility descriptor for 3+3D-QSAR.

M. Dervarics, Ferenc Ötvös, and Tamás A. Martinek* [Inst. of Biochem. & Biol. Res. Cent. of the Hungarian Acad. of Sci.]

J.Chem.Info. & Mod. **46,** 1431-1438 (2006)

3+3D-QSAR approach is used to model the conformational free energy loss with internal coordinate-based flexibility descriptors. The pharmacophore point pair distance descriptors introduced are useful in the construction of QSAR models and in the prediction of important features of the active conformation. The performance of the chiralitysensitive flexibility descriptor is tested on two active series: 37 endomorphin analogues with opiate activity and 38 PGF2α analogues with antinidatory activity. The newly devised descriptor resulted in improved QSAR models in terms of both prediction accuracy and precision of the chiral geometric features of the predicted active conformations.

Conformational Search and Analysis

Conformations of higher Gangliosides and their binding with cholera toxin: Investigation by molecular modeling, molecular mechanics, and molecular dynamics.

D.J. Sundara Sharmila, and K.Veluraja* [Sathyabama Deemed Univ.]

J.Biomol. Stru. & Dynamics. **23,** 641-656 (2006)

Molecular mechanics and MD studies are used to investigate the conformational preference of cell surface higher gangliosides (GT1A and GT1B) and their interaction with Cholera Toxin. The binding site of cholera toxin is shallowed and accommodate a maximum of two NeuNAc residues. The NeuNAc binding site of cholera toxin is an important for the design of inhibitors, that could prevent the infection of cholera.

A!
Ligand bias of scoring functions in structure-based virtual screening.

Micael Jacobsson* [Univ. of Uppsala], and Anders Karlén

J.Chem.Info. & Mod. **46**, 1334-1343 (2006)

A total of 945 known actives and nearly 10,000 decoy compounds are docked to eight different targets, and the resulting poses are scored using 10 different scoring functions. Three different score postprocessing methods are evaluated with respect to improvement of the enrichment in virtual screening. A high to intermediate linear correlation between the score and the number of heavy atoms is found for all scoring functions except FlexX. It is observed that a correlation between the size dependence of a scoring function and the effectiveness of PLS MASC in increasing the enrichment for that scoring function. The results suggested that ligand bias in scoring functions is a source of false positives in structure-based virtual screening.

Potentials and Parameters

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Ion permeation through a narrow channel: Using gramicidin to ascertain all-atom molecular dynamics potential of mean force methodology and biomolecular force fields.

T.W. Allen* [Univ. of Calif.], O.S. Andersen, and Benoit Roux

Biophys. J. **90**, 3447-3468 (2006)

MD simulations are used to investigate the methods for extracting the potential of mean force governing ion permeation. When comparing the modern all-atom force fields of CHARMM27 and AMBER94, it is found that a fairly consistent picture emerges, and that both AMBER94 and CHARMM27 predict observables that are in semi-quantitative agreement with both the experimental conductance and dissociation coefficient. MD-PMF approach is a powerful tool for understanding and predicting the function of narrow ion channels in a manner that is consistent with the atomic and thermally fluctuating nature of proteins.

Amber force field implementation, molecular modelling study, synthesis and MMP-1/MMP-2 inhibition profile of (*R*)- and (*S*)-*N*-hydroxy-2-(*N*-isopropoxybiphenyl-4-ylsulfonamido)-3-methylbutanamides.

Tiziano Tuccinardi, Adriano Martinelli* [Univ. di Pisa], Elisa Nuti, Paolo Carelli, Federica Balzano, Gloria Uccello-Barretta, Gillian Murphy, and Armando Rossello*

Bioorg. Med. Chem. **14**, 4260-4276 (2006)

Ab initio calculations with B3LYP/Lanl2DZ level were performed to determine all the structural and catalytic zinc parameters to study MMPs and their complexes with hydroxamate inhibitors. The obtained parameters were used to study the docking of some known MMPi and the previously described inhibitor, which showed an inhibitory activity for MMP-1, and -2, with the aim of explaining the different selectivity.

Potentials and Parameters (cont'd.)

A new generation of statistical potentials for proteins.

Y. Dehouck* [Univ. Libre de Bruxelles], D. Gilis, and M. Rooman

Biophys. J. **90**, 4010-4017 (2006)

A novel and flexible derivation scheme of statistical, database-derived, potentials is proposed, which allows one to take simultaneously into account specific correlations between several sequence and structure descriptors. The optimal potential is generated as a combination of several coupling terms, measuring correlations between residue types, backbone torsion angles, solvent accessibilities, relative positions along the sequence, and interresidue distances. This potential outperforms all tested residue-based potentials, and even several atom-based potentials.

Water properties from first principles: Simulations by a general-purpose quantum mechanical polarizable force field.

A. G. Donchev, N. G. Galkin, A. A. Illarionov, O. V. Khoruzhii, M. A. Olevanov, V. D. Ozrin, M. V. Subbotin, and V. I. Tarasov* [Algodign, LLC,]

PNAS. **103**, 8613-8617 (2006)

Quantum mechanical polarizable force field (QMPFF) is applied for simulations of liquid water. The results are well agreed with a variety of experimental thermodynamic and structural data, better than that provided by specialized water potentials. QMPFF2 is the only *ab initio* force field to accurately reproduce the anomalous temperature dependence of water density. The ability of this force field is successfully simulating the properties of both organic molecules and water. The results are useful for simulations of proteins and protein–ligand interactions in the aqueous environment.

Molecular Dynamics

The mechanism of TC23O's thermostability: A molecular dynamics simulation study.

Zhi Guo* [Fudan Univ.], Li-Na Xu, and Lin-Xiang Zhou

J.Biomol. Stru. & Dynamics. **23**, 603-612 (2006)

The quasielastic neutron scattering index β and the modulus of a protein's quasi-electric dipole moment are used to study the thermostability of wildtype TC23O and its mutants. Charged residues Arg314, Glu246, Glu291, and some prolines near the C-terminus of the sequence are identified for the thermostability of wildtype TC23O. The molecular conformation changes during the simulation, and is demonstrated how the mutant P228S is destabilized by disrupting two salt-bridges Asp116OD1-Lys215N and Glu210OE1-Lys217N at an adjacent β-turn. The destabilization of P296S showed to intimate correlated with the break down of ion pair Lys188N-Glu291OE1.

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cAMP Modulation of the cytoplasmic domain in the HCN2 channel investigated by molecular simulations.

Marco Berrera, Sergio Pantano, and Paolo Carloni* [Venetian Inst. of Mol.Med.]

Biophys. J. **90**, 3428-3433 (2006)

MD simulations are used to investigate the molecular basis of cAMP channel modulation of a segment comprising the C-linker and the cyclic nucleotide binding domain (CNBD) in the presence and absence of cAMP, through HCN2 crystal structure from mouse. In presence of cAMP, the protein undergoes an oscillation of the quaternary structure on the order of 10 ns, not observed in the apoprotein. It is proposed that the cAMP-triggered large-scale oscillation plays an important role for the channel's function, being coupled to a motion of the C-linker which, in turn, modulates the gating of the channel.

Molecular Dynamics (cont'd)

Novel changes in discoidal high density lipoprotein morphology: A molecular dynamics study.

Andrea Catte, J.C. Patterson, M.K. Jones, W.G. Jerome, D. Bashtovyy , Z. Su, Feifei Gu, Jianguo Chen, M.P. Aliste, S.C. Harvey, Ling Li , G. Weinstein, and J.P. Segrest* [Cent. for Comp.and Stru. Biol.]

Biophys. J. **90**, 4345-4360 (2006)

MD simulations on a series of progressively smaller discoidal high density lipoprotein particles produced by incremental removal of palmitoyloleoylphosphatidyl-choline via four different pathways. The starting model contained 160 palmitoyloleoylphosphatidylcholines and a belt of two antiparallel amphipathic helical lipid-associating domains of apolipoprotein A-I. The results provided atomic resolution models for two of the particles produced by in vitro reconstitution of nascent high density lipoprotein particles.

QM/MM

Ab initio and molecular dynamics studies of crystalline TNAD (*trans*-1,4,5,8-Tetranitro-1,4,5,8-tetraazadecalin).

Ling Qiu, He-Ming Xiao* [Nanjing Univ. of Sci. & Tech.], Wei-Hua Zhu, Ji-Jun Xiao, and Wei Zhu

J. Phys. Chem. B. **110**, 10651 -10661 (2006)

DFT calculations are used to study the structural and electronic properties of the energetic crystal TNAD (*trans*-1,4,5,8-tetranitro-1,4,5,8- tetraazadecalin). The predicted crystal structure is well agreed with the experimental data and there are strong inter- and intramolecular interactions in bulk TNAD. MD simulations are used to determine the average lattice parameters and elastic properties as functions of temperature.

The Poulos-Kraut mechanism of compound I formation in horseradish peroxidase: A QM/MM study.

Etienne Derat, and Sason Shaik* [Hebrew Univ. of Jerusalem]

J. Phys. Chem. B. **110**, 10522 -10533 (2006)

QM/MM calculations are used to elucidate the Poulos-Kraut mechanism of O-O bond activation and Compound I formation in HRP, in conditions corresponding to neutral to basic pH. The lowest energy mechanism is involving initial deprotonation of ferric hydrogen peroxide complex (involving spin crossover from the quartet to the doublet state) by His42 to form ferric-hydroperoxide (Cpd 0).

Ab initio calculations of dispersion coefficients for nucleic acid base pairs.

T.P. Haley* [Univ. of Miami], E.R. Graybill, and S.M. Cybulski

*J. Chem.Phys.***124,** 204301 -204306 (2006)

Ab initio calculations are used for two- and three-body dispersion coefficients for the four most important nucleic acid bases. Hartree-Fock approach and the aug-cc-pVDZ basis set is used to identify the isotropic as well as anisotropic coefficients. Single and double excitation coupled-cluster theory with noniterative treatment of triple excitations [CCSD(T)] was used to find the values of static polarizabilities, which are subsequently used to estimate the values of the CCSD(T) dispersion coefficients.

Assessing the protonation state of drug molecules: The case of aztreonam.

Natalia Díaz, T.L. Sordo, Dimas Suárez * [Univ. de Leon], Rosa Méndez, J. Martín Villacorta, Luis Simón, M. Rico, and M. Angeles Jiménez

J. Med. Chem. **49**, 3235 -3243 (2006)

ONIOM(HF/3-21G*:AMBER), B3LYP/6-31+G** approximations are used for geometry relaxation, and for electronic and electrostatic solvation energies respectively, molecular mechanics is used for attractive dispersion energy in the energy calculations. The value of the free energy of solvation of a proton is treated as a parameter and chosen to give the best match between calculated and experimental pK_a values for small molecules. This computational scheme will give satisfactory results in the pK_a calculations for drug molecules.

QM/MM (cont'd)

Combining quantum mechanics methods with molecular mechanics methods in ONIOM.

Thom Vreven* [Gaussian Inc.,], K. Suzie Byun, Istvἀn Komἀromi, Stefan Dapprich, John A. Montgomery, Jr., Keiji Morokuma, and Michael J. Frisch

J. Chem. Theory. & Comp. **2**, 815 -826 (2006)

ONIOM (QM:MM) approximation for the electrostatic interaction between the regions is included at the classical level and the extension to electronic embedding is presented. The results showed that the behavior of ONIOM with electronic embedding is more stable than QM/MM with electronic embedding. The link atom correction, which is implicit in ONIOM but not in QM/MM is also investigated and practical aspects of ONIOM(QM:MM) calculations are demonstrated.

Theoretical calculation of hydrogen-bonding strength for drug molecules.

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

J. Chem. Theory. & Comp. **2**, 863 -872 (2006)

A computational method is developed based on DFT calculation to predict the hydrogen-bonding strength for different acceptors with respect to a given donor. The results are well agreed with the calculated hydrogen-bonding energies and are useful for evaluating the effects of steric interference and inhibitor binding geometry on hydrogen-bonding strength in drug design.

Modelling of carbohydrate-aromatic interactions: Ab initio energetics and force field performance.

V. Spiwok* [Inst. of Chem. Tech. in Prague], P. Lipovová, T. Skálová, E. Vondráčková, J. Dohnálek, J. Hašek, and B. Králová

J.Comp.Aided Mol. Design. **19**, 887-901 (2006)

Ab initio interaction energies for 20 carbohydrate–aromatic complexes taken from 6 selected X-ray structures of glycosidases and carbohydrate-binding proteins are calculated. All interaction energies of a pyranose moiety with a side chain of an aromatic residue were calculated as attractive with interaction energy as calculated at the MP2/6-311+G(d) level. The interaction energies calculated at MP2 level are compared with MM force fields (OPLS,GROMOS,CSFF/CHARMM, HEAT/CHARMM, Glycam/AMBER, MM2 and MM3). The results showed that MM calculated interaction energies are supporting the application of MM methods in the area of glycochemistry anf glycobiology.

Intra- and intermolecular interactions between cyclic-AMP receptor protein and DNA: *Ab initio* fragment molecular orbital study.

Kaori Fukuzawa* [Mizuho Info. & Res.Inst., Inc.], Yuto Komeiji, Yuji Mochizuki, Akifumi Kato, Tatsuya Nakano, and Shigenori Tanaka

J.Comp. Chem. **27**, 948-960 (2006)

AMBER-94 force field and at the HF and MP2 levels are used to investigate the sequence-specific binding and the stability of the DNA duplex of the cAMP receptor protein (CRP) complexed with a cAMP and DNA duplex. In the interaction between DNA and CRP-cAMP, there is a significant charge transfer from the DNA to CRP, and this CT interaction has an important role as well as the electrostatic interactions.

DIESEL-MP2: A new program to perform large-scale multireference-MP2 computations.

Patrick Musch, and Bernd Engels* [Univ. of Wuerzburg]

J.Comp. Chem. **27**, 1055-1062 (2006)

A new program MR-MP2 is developed based on DIESEL program. This program is applied for systems with 400-500 basis functions and more than 100 electrons. It possesses two integral interfaces MOLCAS and TURBOMOLE and the efficiencies of the codes obtained are compared with GNU or Intel compilers.

Comparative or Homology Modeling

Active site acidic residues and structural analysis of modelled human aromatase: A potential drug target for breast cancer.

J. Narashima Murthy, M. Nagaraju, G. Madhavi Sastry, A. Raghuram Rao, and G. Narahari Sastry* [Indian Inst. of Chem. Tech.]

J.Comp.Aided Mol. Design. **19**, 857-870 (2006)

Homology Modeling, docking and molecular dynamics are used to study the lining cavity of eight acidic residues. The results showed that the environment of the residues E245, E302 and D222 is most suitable for carboxylate ion formation in the uncomplexed form. The stability of D309, D222 and D476 anions is to increase on complexation to steroidal substrates. The inhibition of aromatase activity by 4-hydroxy androstenedione (formestane) is attributed to a critical hydrogen bond formation between the hydroxy moiety and T310/D309 as well as the large distance from D476. The results correlated well with earlier site directed mutagenesis studies.

Ligand Docking

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

Fabrizio Manetti, Giada A. Locatelli, Giovanni Maga, Silvia Schenone, Michele Modugno, Stefano Forli, Federico Corelli, and Maurizio Botta* [Univ. of Genova]

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

Docking and MD simulations are used to build the 3D-models of the complexes between Src and several of its known inhibitors. Interactions most contributing to activity of the inhibitors, in terms of hydrogen bonds and hydrophobic contacts, are codified into pharmacophoric models. The results indicated that 1,3,4-thiadiazoles and pyrazolydine-3,5-diones showing inhibitory activity in the submicromolar range in a cell-free assay toward Src. The identified hits toward Abl tyrosine kinase are tested and finding activity in the submicromolar range. The biological data suggested that the computational protocol is an efficient tool for identifying new hits toward both Src and Abl.

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

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

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

MolDock, a new molecular docking algorithm is introduced, which 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 (PLP) including new hydrogen bonding and electrostatic terms. The docking accuracy of MolDock is evaluated by docking flexible ligands to 77 protein targets, able to identify the correct binding mode of 87% of the complexes.

A!
Protein farnesyltransferase: Flexible docking studies on inhibitors using computational modeling.

Wayne C. Guida* [Univ. of South Florida], A.D. Hamilton, J.W. Crotty, and S.M. Sebti

J.Comp.Aided Mol. Design. **19**, 871-885 (2006)

MacroModel is used for docking peptide, peptidomimetic and non-peptidomimetic inhibitors of the zinc metalloenzyme, farnesyltransferase, into the enzyme binding site. Inhibitor flexibility, farnesyl pyrophosphate substrate flexibility, and partial protein flexibility are taken into account in the docking studies. It is found that numerous alternative conformations for the methionine side chain is accommodated by the enzyme suggested that the methionine pocket could tolerate groups larger than methionine at the C-terminus of the tetrapeptide, which suggested alternative locations for the placement of side chains that may improve potency.

Ligand Docking (Cont'd)

Modeling the structural basis of human CCR5 chemokine receptor function: From homology model building and molecular dynamics validation to agonist and antagonist docking.

A. Fano, D. W. Ritchie, and A. Carrieri* [Univ. of Aberdeen]

J.Chem.Info. & Mod. **46**, 1223-1235 (2006)

Homology modeling is used to construct and validate a 3D-model of the human CCR5 receptor from the X-ray structure of the bovine rhodopsin receptor. The model is examined through MD and docking simulations using both natural agonists and a synthetic antagonist. The results gave an explanation for structural basis for the recognition, activation, and inhibition processes of CCR5 and may provide fresh insights for the design of HIV-1 entry blockers.

Protein Structure Prediction

Gaussian-Weighted RMSD superposition of proteins: A structural comparison for flexible proteins and predicted protein structures.

K.L. Damm, and H.A. Carlson* [Univ. of Michigan]

Biophys. J. **90**, 4558-4573 (2006)

A novel method is developed to overlay two protein conformations by their atomic coordinates using a Gaussian-weighted RMSD (wRMSD) fit. The algorithm is based on the Kabsch least-squares method and determines an optimal transformation between two molecules by calculating the minimal weighted deviation between the two coordinate sets. Finally, it was showed that how wRMSD fits can be used to evaluate predicted protein structures.

Side-chain interactions determine amyloid formation by model polyglutamine peptides in molecular dynamics simulations.

A.J. Marchut, and Carol K. Hall* [North Carolina State U.]

Biophys. J. **90**, 4574-4584 (2006)

MD simulations are used to study the polyglutamine-containing proteins misfold and aggregate processes. PRIME is an off-lattice, unbiased, intermediate-resolution protein model based on an amino acid representation of between three and seven united atoms, depending on the residue being modeled. The results showed that the spontaneous formation of aggregates and annular structures that are made up of β-sheets starting from random configurations of random coils.

Surface and Volume Determination

Assessing implicit models for nonpolar mean solvation forces: The importance of dispersion and volume terms.

J.A. Wagoner, and Nathan A. Baker* [Washington U.]

PNAS. **103,** 8331-8336 (2006)

The solvent-accessible surface area model with additional volume and dispersion integral terms suggested by scaled particle models and Weeks–Chandler–Andersen theory is presented. This more complete nonpolar implicit solvent model shows very good agreement with explicit solvent results and suggested that the inclusion of appropriate dispersion and volume terms are essential for an accurate implicit solvent description of atomic-scale nonpolar forces.

Molecular Graphics

Visualization of large-scale aqueous solubility data using a novel hierarchical data visualization technique.

Fumiyoshi Yamashita* [Kyoto Univ.], Takayuki Itoh, Hideto Hara, and Mitsuru Hashida.

J.Chem.Info. & Mod. **46,** 1054-1059 (2006)

HeiankyoView, a novel hierarchical data visualization technique is introduced to visualize large-scale multidimensional chemical information. HeiankyoView is applied to visualize aqueous solubility data for 908 compounds collected from the literature. The results of a recursive partitioning analysis and hierarchical clustering analysis are visualized, the trends hidden in the solubility data is effectively displayed as intuitively understandable visual images. This is a powerful tool to help us to understand structure-activity relationship from a large-scale data set.

Enhancing specificity and sensitivity of pharmacophore-based virtual screening by incorporating chemical and shape features-A case sudy of HIV protease inhibitors.

Deepangi Pandit, Sung-Sau So, and Hongmao Sun* [Hoffmann-La Roche]

J.Chem.Info. & Mod. **46**, 1236-1244 (2006)

This study is emphasizing to achieve improved specificity and sensitivity of pharmacophore-based virtual screening. Human immunodeficiency virus protease and its inhibitors (PIs) are used, including the selection of chemical features, involvement of excluded volumes (EV), the tolerance radius of excluded volumes, energy windows, and the maximum number of conformers in conformation generation. Protein flexibility is simulated by adjusting the sizes of EV. The best pharmacophore model, combining both chemical features and excluded volumes, is able to correctly identify 60 out of 75 structurally diverse known PIs, while misclassifying only 5 out of 75 similar compounds that are not inhibitors.

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

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

917-925 **Energy density analysis of cluster size dependence of surface-molecule interactions (II): Formation adsorption onto a Cu(111) surface,** Hiromi Nakai*[Waseda Univ.], and Yasuaki Kikuchi

Energy Density Analysis (EDA) for the largest model cluster Cu_{56} showed that the adsorption-induced energy density variation in Cu atoms decays with distance from the adsorption site.

926-932 **Starting SCF calculations by superposition of atomic densities,** J.H. Van Lenthe * [Utrecht Univ.], R. Zwaans, H.J.J. Van Dam, M.F. Guest

The procedure is described to start an SCF calculation of the general type from a sum of atomic electron densities.

933- 940 **Theoretical study on the isomeric structures and the stability of silylenoid (Tsi)Cl$_2$SiLi (Tsi = C(SiMe$_3$)$_3$),** Ju Xie, Dacheng Feng * [Shandong Univ.] , and Shengyu Feng

DFT theory at the B3LYP/6-31G(d) basis set is used to study the structures and isomerization of silylenoid (Tsi)Cl$_2$SiLi (Tsi = C(SiMe$_3$)$_3$).

941-947 **Rapidly convergent procedure to solve the density profile equation in the classical density functional theory**, Shiqi Zhou* [Zhuzhou Inst. of Tech.]

Broyden method is described by using classical DFT to solve the density profile equation.

948-960 **Intra- and intermolecular interactions between cyclic-AMP receptor protein and DNA: Ab initio fragment molecular orbit al study**, Kaori Fukuzawa* [Mizuho Info. & Res. Inst. Inc.,], Yuto Komeiji, Yuji Mochizuki, Akifumi Kato, Tatsuya Nakano, Shigenori Tanaka.

The *ab initio* fragment molecular orbital (FMO) calculations are performed for the cAMP receptor protein (CRP) complexed with a cAMP and DNA duplex to elucidate their sequence-specific binding and the stability of the DNA duplex.

961-965 **On the joint time-frequency characteristics of chemical oscillations,** K. Darowicki, and W. Felisiak* [Gdansk Univ. of Tech.]

A method of time-frequency transformations of nonstationary signals is discussed and applied to the analysis of oscillatory Belousov - Zhabotinsky (BZ) reaction.

966-975 **Determination of the ΔpKa between the active site cysteines of thioredoxin and DsbA,** Alexandra T. P. Carvalho, P. A. Fernandes, and Maria J. Ramos* [Univ. do Porto]

QM/MM methods are used to compare and characterize the active site dithiols of both enzymes, responsible for the large differences in pKa and redox potential between two homologous enzymes, thioredoxin and DsbA.

976-985 **The polarizable continuum model (PCM) interfaced with the fragment molecular orbital method (FMO),** Dmitri G. Fedorov* [Nat.Inst.of Adv. Indu. Sci. & Tech.], Kazuo Kitaura, Hui Li, Jan H. Jensen, and Mark S. Gordon.

Fragment molecular orbital / polarizable continuum model (FMO/PCM), is applied to a set of model systems, including α-helices and β-strands of alanine consisting of 10, 20, and 40 residues and their mutants to charged arginine and glutamate residues.

986-993 **Royal crown-shaped electride Li_3-N_3-Be containing two superatoms: New knowledge on aromaticity,** Zhi-Ru Li* [Zilin Univ.], Fang-Fang Wang, Di Wu, Ying Li, Wei Chen, Xiao-Ying Sun, Feng Long Gu, and Yuriko Aoki.

The structure and aromaticity of a royal crown-shaped molecule Li_3-N_3-Be are studied at the CCSD(T)/aug-cc-pVDZ level. It is found that the Li_3^{2+} ring exhibits aromaticity mainly because the Li_3^{2+} ring can share the π- electron with the N_3^{-3} ring.

Journal of Computational Chemistry 27(9), 15th July, 2006

995-1008 **On the efficient evaluation of fourier patterns for nanoparticles and clusters,** Antonio Cervellino* [Lab. for Neutron Scattering], Cinzia Giannini, Antonietta Guagliardi

In the present work, how to encode the enormous array of interatomic distances to a much smaller array of equispaced values on a coarse grid, how to perform a fast computation of the diffraction pattern from this equispaced grid and how to optimize the grid step to obtain an arbitrarily small error on the computed diffraction pattern are discussed.

1009-1019 **Half-numerical evaluation of pseudopotential integrals,** Roberto Flores-Moreno* [Avenida Inst. Polit. Nacional], Rodrigo J.Alvarez-Mendez, Alberto Vela, and Andreas M. Köster

A half-numeric algorithm for the evaluation of effective core potential integrals over Cartesian Gaussian functions is described. Local and semilocal integrals are separated into two-dimensional angular and one-dimensional radial integrals.

1120-1032 **An agent-based system to discover protein-protein interactions, identify protein complexes and proteins with multiple peptide mass fingerprints,** Tzong-Yi Lee , Jorng-Tzong Horng*[Nat. Cent. Univ.], Hsueh-Fen Juan , Hsien-Da Huang, Li-Cheng Wu , Meng-Fong Tsai, Hsuan-Cheng Huang**.**

An agent-based system, AgentMultiProtIdent, which integrated two protein identification tools and a variety of databases storing relations among proteins and used to discover protein-protein interactions and protein functional associations, and identify protein complexes.

1033-1044 **T-cell epitopes of the La/SSB autoantigen: Prediction based on the homology modeling of HLA-DQ2/DQ7 with the insulin-B pepti de/HLA-DQ8 complex,** A. Kosmopoulou, M. Vlassi, Athanassios Stavrakoudis * [Univ. of Ionnina], Constantinos Sakarellos, and M. Sakarellos-Daitsiotis.

Homology modeling is used to build DQ2 and DQ7 based on the structures of HLA-DQ2 and DQ7 molecules as templates. The quality and reliability of the modeled DQ2 and DQ7 is confirmed by the Ramachandran plot and the TINKER molecular modeling software.

1045-1053 **Ab initio potential energy surface and predicted microwave spectra for Ar-OCS dimer and structures of Arn-OCS (n = 2-14) clusters**, Hua Zhu, Yong Guo, Ying Xue, Daiqian Xie

The results showed that there are two minima corresponding to one distorted tetrahedral structure and one planar structure for the ternary complex. The 14 nearest neighbor Ar atoms form the first solvation shell around the OCS molecule.

Journal of Computational Chemistry 27(10), 30th July, 2006

1055-1062 **DIESEL-MP2: A new program to perform large-scale multireference-MP2 computations**, Patrick Musch, and Bernd Engels* [Univ. of Wuerzburg]

See **Methodology/QM/MM**

1063-1070 **Electric field-derived point charges to mimic the electrostatics in molecular crystals**, A.E. Whitten, J. J. McKinnon, and Mark A. Spackman* [Univ. of Western Australia]

A novel method is presented for determining atomic charges for a molecule in a crystal based on a fit to the electric field at points on a surface around the molecule.

1071-1075 **Dramatic performance enhancements for the FASTER optimization algorithm,** B.D. Allen, and Stephen L. Mayo* [California Inst. of Tech.]

See **Applications/Bioinformatics**

1076-1087 **Definition of Systematic, Approximately Separable, and Modular Internal Coordinates (SASMIC) for macromolecular simulation,** Pablo Echenique* [Univ. de Zaragoza], and J. L. Alonso.

See **Applications/Bioinformatics**

1088-1092 **Anion substitution in zinc chalcogenides,** Karl Jug* [Univ. of Hannover], and V.A. Tikhomirov. MSINDO, a semiempirical molecular orbital method is used to study the anion substitution effects on the structure and energy of zinc chalcogenides.

1093-1100 **The Jahn-Teller and pseudo-Jahn-Teller effects in the anion photoelectron spectroscopy of B_3**

cluster, T. S. Venkatesan, K. Deepika, S. Mahapatra* [Univ. of Hyderabad]

Quantum dynamical approach is used to study the photodetachment spectroscopy of $\overline{B3}$ anion and the results are compared with the experimental photoelectron spectra of $B\overline{3}$. Both $B\overline{3}$ and B_3 possess D_{3h} symmetry at the equilibrium configuration of their electronic ground state.

1101-1111 **RM1: A reparameterization of AM1 for H, C, N, O, P, S, F, Cl, Br, and I,** G.B. Rocha, R.O. Freire, Alfredo M. Simas* [CCEN], and J.J.P. Stewart

RM1 (Recife Model 1): a reparameterization of AM1 model is presented by considering the elements: C, H, N, O, P, and S, and halogens. The training set consisted of 1736 molecules, representative of organic and biochemistry, containing C, H, N, O, P, S, F, Cl, Br, and I atoms.

1112-1118 **Ratio control variate method for efficiently determining high-dimensional model representations,** Genyuan Li, and Herschel Rabitz* [Princeton Univ.]

RS (Random Sampling)-HDMR is a practical form of HDMR based on randomly sampling the overall function, and utilizing orthonormal polynomial expansions to approximate the RS-HDMR component functions.

Current Opinion in Structural Biology, 16(2), April,2006.

142-151 **Electrostatics calculations: latest methodological advances** , Patrice Koehl* [Univ. of California] Implicit solvent models with Poisson-Boltzmann equation and generalized born approaches are included in molecular dynamics simulations and their accuracies are assessed by comparing with the experimental data.

152-159 **Water structure and interactions with protein surfaces**, Tanya M Raschke* [Stanford Univ.]. The subtle changes in the structure of hydration water is investigated by theoretical studies.

160-165 **Conformer generation under restraints**, P. IW de Bakker, N. Furnham, T.L. Blundell, and Mark A DePristo* [Harvard Univ.]

Conformational sampling is used for structure prediction as the bottleneck in accurate prediction shifts from energy functions to the methods used to find low-energy conformers.

166-171 **In quest of an empirical potential for protein structure prediction**, Jeffrey Skolnick* [Univ. of Buffalo] Recent advances in empirical potentials are allowed to predict the structures relative to their initial template alignments over a wide range of target-template homology.

172-177 **Comparative modeling for protein structure prediction**, Krzysztof Ginalski*[Warsaw Univ.] Comparative modeling based on more than 30% sequence identity is now approaching its natural template-based limits and further improvements require the development of effective refinement techniques capable of driving models toward native structure.

178-182 **Servers for protein structure prediction,** Daniel Fischer* [State Univ. of New York at Buffalo] The structural genomics and genome sequencing projects, and significant improvements in the performance of protein structure prediction methods, a generation of automated servers has evolved.

183-193 **High-resolution protein-protein docking**, Jeffrey J Gray* [Johns Hopkins Univ.]

The high-resolution prediction of protein-protein docking is created structures with atomic-level accuracy, improves the rapid sampling of conformations and increased accuracy of binding free energy calculations.

194-200 **Flexible protein-protein docking,** Alexandre MJJ Bonvin* [Utrecht Univ.] Novel approaches are emerged involving collective degrees of motion, multicopy representations and

multibody docking, which allowed larger conformational changes to be modeled.

201-203 **Macromolecular assemblages**, Edward H Egelman* [Univ. of Virginia] and Andrew GW Leslie.

204-212 **Structure and function of myosin filaments**, Roger Craig* [Univ. of Massachusetts Med.Sch.], and J.L. Woodhead.

Docking of atomic structures into cryo-EM density maps suggests how regulated myosin filaments are 'switched off', bringing about muscle relaxation. The sequence analysis suggests probable interactions between myosin tails in the backbone, whereas crystallographic and EM studies are starting to reveal tail interactions directly in three dimensions.

213-220 **Chromatin architecture**, Christopher L Woodcock* [Univ. of Massachusetts]

X-ray diffraction, NMR spectroscopy, electron microscopy and atomic force microscopy studies are provided valuable insights into the structural roles of histone variants, the impact of histone mutations and the compaction of nucleosomal arrays.

221-229 **Structural mechanisms underlying nucleotide-dependent self-assembly of tubulin and its relatives,** Eva Nogales* [Univ. of California] and Hong-Wei Wang
The present studies revealed the similarities and differences between these structures and their possible functional implications.

230-236 **The mechanism of pore formation by bacterial toxins,** Sarah J Tilley and Helen R Saibil* [Birkbeck Coll.]

The pore-forming toxins typically transform from soluble, monomeric proteins to oligomers that form transmembrane channels.

237-244 **Karyopherin flexibility in nucleocytoplasmic transport,** Elena Conti, Christoph W Müller and Murray Stewart***** [MRC Lab.of Mol. Biol.]

The nuclear transport factors of the importin-β superfamily of karyopherins showed that these proteins are superhelices of HEAT repeats that are able to assume different conformations in different functional states.

245-251 **Mass spectrometry of macromolecular assemblies: preservation and dissociation**, J.LP Benesch and Carol V Robinson* [Univ. of Cambridge]

The use of gas phase dissociation to probe oligomeric organization and topology, and increased understanding of the electrospray process is leading to knowledge of the structure of protein assemblies both in solution and in the gas phase.

252-259 **Structure of the rhodopsin dimer: a working model for G-protein-coupled receptors**, D. Fotiadis, B. Jastrzebska, A. Philippsen, D.J. Müller, K. Palczewski, and Andreas Engel* [Univ. of Basel]

Recent functional analyses of fractions from solubilized disk membranes revealed that higher-order Rho oligomers are the most active species. These results enhanced the understanding of GPCR structure and function.

260-265 **Recent atomic models of amyloid fibril structure**, R. Nelson and David Eisenberg* [Howard Hughes Med. Inst.]

The gain-of-interaction models is subdivided into direct stacking, cross-β spine, three-dimensional domain swapping and three-dimensional domain swapping with a cross-β spine.

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.

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