Indo-German Workshop on Computing in Chemistry, Biology and Medicine

29–30 November 2017
Venue: IIIT Hyderabad

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INTERNATIONAL INSTITUTE OF INFORMATION TECHNOLOGY
HYDERABAD

Indo-German Workshop on Computing in Chemistry, Biology and Medicine 2017, IIIT Hyderabad

(CCBM 2017)

November 29-30, 2017

ABSTRACT BOOK

Computing in Chemistry, Biology and Medicine 2017, IIIT Hyderabad

Programm

November 29: Day 1	
1:30 to 2:30 PM	**Registration**
2:30 to 3:00 PM	**Inauguration**
	P. J. Narayanan, IIIT-H
	Abhijit Mitra, CCNSB, IIIT-H
	Neel Sarovar Bhavesh, Lindau alumni, ICGEB
	Ingrid Krüßmann, Division of International Affairs, DFG
	Nikolaus Turner, Council/Foundation, Lindau Nobel Laureate Meetings
Session 1 (Chair: K. V. R. Chary, TIFR)	
3:00 to 3:30 PM	Holger Gohlke, Univ. Düsseldorf
3:30 to 4:00 PM	Neelanjana Sengupta, IISER Kolkata
Session 2 (Jagannath Mondal, (TIFR), Neel Bhavesh, (ICGEB), & Biswarup Pathak, (IIT Indore))	
4:30 to 6:00 PM	Tea break followed by Poster Session - I
Session 3 (Chair: Susanta Mahapatra, UoHyd)	
5.30 to 6.00 PM	Govardhan Reddy, IISc
6:00 to 6:30 PM	Shachi Gosavi, NCBS
6:30 to 7:00 PM	G. Rajaraman, IIT Bombay
7:30 pm onwards	Banquet at Ella Hotels

November 30: Day 2	
Session 4 (Chair: Lalitha Guruprasad, UoHyd)	
9:00 to 9:30 AM	Biswarup Pathak, IIT Indore
9:30 to 10:00 AM	K. R. S. Chandrakumar, BARC
10:00 to 10:15 AM	Sunita Patel, UM-DAE
Session 5 (Jagannath Mondal, (TIFR), Neel Bhavesh, (ICGEB), & Biswarup Pathak, (IIT Indore))	
10:30 to 12:00 PM	Tea break followed by Poster Session – II
Session 6 (Chair: R. Thenmalarchelvi, IIT Hyderabad)	
12:00 to 12:30 PM	Petra Imhof, Freie Univ.
12:30 to 1:00 PM	Nisanth Nair, IIT Kanpur
1:00 to 2:15 PM	Lunch at IIIT Guest House
Session 7 (Chair: Durba Roy, BITS)	
2:30 to 3:00 PM	Yasha Hasija, DTU
3:00 to 3:30 PM	Prasad V Bharatam, NIPER Mohali
Session 8	
3:30 to 4:30 PM	Panel Discussion
	G. Narahari Sastry, IICT Hyderabad
	B. Gopalakrishnan, TCS Innovation Labs
	Anu Acharya, Map my genome
	Holger Gohlke, Univ. Düsseldorf
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	Harjinder Singh, IIIT-H
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Supercomputing at the molecular level for the human brain

IL1

Benedikt Frieg[1,4], Christoph Gertzen[1,2], Boris Görg[2], Verena Keitel[2], Claus Seidel[3], Dieter Häussinger[2], **Holger Gohlke**[1,4]

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The brain can be characterized by a vertical hierarchy of neural functioning, from behavior to genetic mechanisms via the (bio)molecular level. Although apparently distinct, these levels cannot be separated because information that exists at one level must be considered in concert with information from all other levels to generate a coherent picture of brain functioning.
Here, we describe the development and application of integrative modeling approaches to tightly link molecular simulations at the atomistic level with sophisticated experiments in order to reveal the molecular underpinning of brain function. In particular, we will address mechanisms of deactivation of glutamine synthetase, which catalyzes the ATP-dependent ligation of ammonia and glutamate to glutamine and, thus, is essential for nitrogen metabolism [1]. We will show how, starting from patient data, one can derive suggestions for a potential personalized treatment counteracting the effect of function-impeding mutations. Furthermore, we will address how oligomer structures of GPCRs, a major class of transmembrane receptors and drug targets, can be revealed in live cells [2] by means of integrating high-precision FRET experiments and molecular simulations [3]. In all, our results show how detailed mechanistic insights and valuable experimental guidance can be derived from molecular simulations, while experimental studies provide necessary validation and helpful restraints for computational studies.

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[2] A. Greife, S. Felekyan, Q. Ma, C. G. W. Gertzen, L. Spomer, M. Dimura, T. O. Peulen, C. Wöhler, D. Häussinger, H. Gohlke, V. Keitel, C. A. M. Seidel, *Sci. Rep.* **2016**, *6*, 36792.
[3] aS. Kalinin, T. Peulen, S. Sindbert, P. J. Rothwell, S. Berger, T. Restle, R. S. Goody, H. Gohlke, C. A. M. Seidel, *Nature Methods* **2012**, *9*, 1218-1225; bM. Dimura, T. O. Peulen, C. A. Hanke, A. Prakash, H. Gohlke, C. A. M. Seidel, *Curr. Opin. Struct. Biol.* **2016**, *40*, 163-185.

Modulating Early Self-Assembly Pathways in an Amyloidogenic Protein: Harnessing the "Computational Microscope"

IL2

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With the advent of enhanced computational power, molecular dynamics (MD) simulations has emerged as an indispensable tool to probe the thermodynamic and kinetic underpinnings of 'soft matter' behaviour. In particular, the myriad superposition of short- and long- ranged interactions that underlie complex biomolecular phenomena such as folding, stability, self-assembly, and surface interactions manifest themselves in the sampled phase space, and can be analyzed to elicit information that may often be compared with experimental data. In this talk, I will highlight some of our recent efforts to understand the early self-assembly of an intrinsically disordered protein, Amyloid beta (Aβ), which is intricately associated with the onset and prognosis of the neurodegenerative Alzheimer's disease (AD). Understanding the detailed mechanisms behind Aβ self-assembly may help in the design of novel therapeutics for AD. Our work on modulation of this protein's self-assembly with carbon nanomaterials has further demonstrated how surface topography is likely to play a role in general protein stability and adsorption. Finally, I will discuss how complementary experiments and simulations yield insights into the plausible association of diabetes with AD by showing how post-translational glycation of Aβ rapidly enhances its self-assembly and fibrillogeneis.

Osmolyte Effects on Aggregation

IL3

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Understanding the role of naturally occurring protective osmolytes on the growth of amyloid fibrils can play an important role in designing strategies to prevent fibril growth. The effect of trimethylamine N-oxide (TMAO) on the growth of amyloid fibrils formed by the Sup35 prion peptide NNQQNY is studied using molecular dynamics simulations. The free-energy surface for the growth of the protofibril shows three major basins, corresponding to the free state where the peptide is in solution, the docked state where the peptide in solution interacts with the surface of the protofibril, and the locked state where the peptide is tightly bound to the protofibril, becoming a part of the fibril. The free-energy surface in the presence of TMAO shows that TMAO stabilizes the locked state of the peptide compared with the free state, indicating that TMAO aids in fibril growth. Dissecting the interaction of TMAO with individual amino acids in the peptide shows that TMAO interacts both directly and indirectly with the amino acids, depending on the nature of the side chains. The methyl groups in TMAO interact strongly with the hydrophobic aromatic ring in the Tyr residue. In the locked state, the surface area of Tyr available for interaction with TMAO decreases; as a result, the Tyr residue in the peptide flips out from the locked position, increasing the fluctuations of the peptide locked in the protofibril. Such strong direct interactions of amino acids with TMAO destabilize the folded or aggregated states of proteins. The overall increased stability of the peptide locked in the protofibril by TMAO is due to entropic or indirect interactions with the backbone Asn and Gln residues, which form major components of the NNQQNY peptide.

Understanding hydrogen-deuterium exchange data using protein simulations

IL4

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Hydrogen deuterium exchange (HDX) coupled with either nuclear magnetic resonance (NMR) or mass spectrometry (MS) can be used to probe protein stability and dynamics. In order to gain a theoretical understanding of HDX and in turn, protein dynamics, the rates of HDX have been correlated with protein structural parameters like solvent access, atomic depth within the structure, etc. However, individually, these parameters have been found to have patchy correlations with experimental data. We computationally examine the simpler problem of differentiating between those amides whose dynamics are visible through HDX experiments and those which exchange so fast that they have already exchanged on the time scale of the experiment. We perform short atomistic molecular dynamics (MD) simulations of three representative proteins, calculate several previously proposed structural parameters from these simulations and compare them with experimental data. Although no individual parameter explains the experimental HDX data completely, combinations of parameters give near-complete agreement. The mechanism of HDX includes several physical processes and our results show that diverse structural parameters may be required to capture the combined effect of all these steps.

Modelling Magnetic Anisotropy in Molecular Magnets

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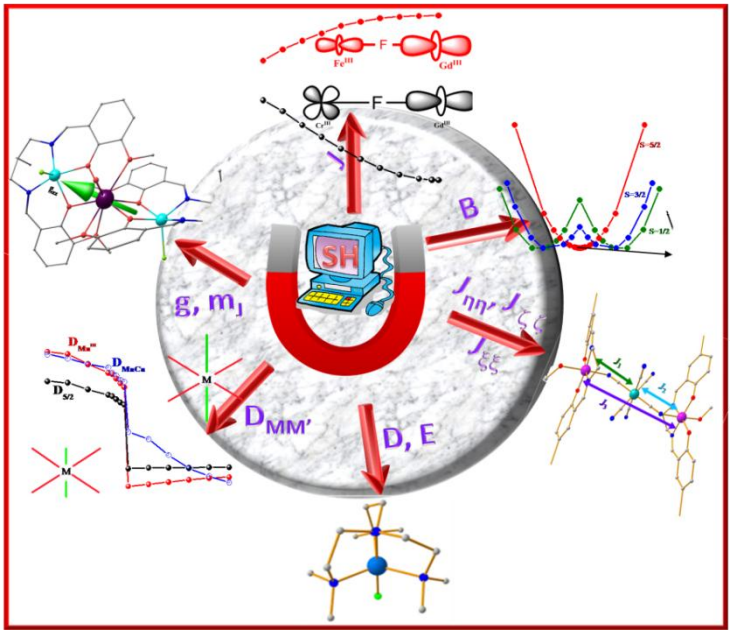
IL5

Molecular magnetism is one of the vastly growing research fields with an aim to design the molecules and materials with tunable magnetic and electronic properties.**Error! Reference source not found.** Their synthesis, characterization and implementation as devices which creates lively crossroad among chemistry, physics and material science: a multidisciplinary research field. These molecules have wide spread potential applications ranging from magnetic storage devices, spintronics, Q-bits in quantum computing to magnetic coolants.**Error! Reference source not found.** Single-molecule magnets (SMMs) are the molecules which show slow relaxation of magnetization below the critical temperature and exhibit hysteresis loop similar to classical magnets. SMMs offer key advantage over classical magnets due to their light weight, solubility and multifunctional behavior. Theoretical tools are indispensable in this arena[2] for understanding the observed magnetic properties. The strength of these methods is not only limited rationalization but also to predict novel molecules which can exhibit superior magnetic properties. In this presentation, I will research effort undertaken in our group towards achieving this goal.[2]



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Carbon Based Electrodes for Ultrafast Al-ion Battery

Preeti Bhauriyal, Arup Mahata, **Biswarup Pathak***

Discipline of Chemistry, IIT Indore, Indore, India;
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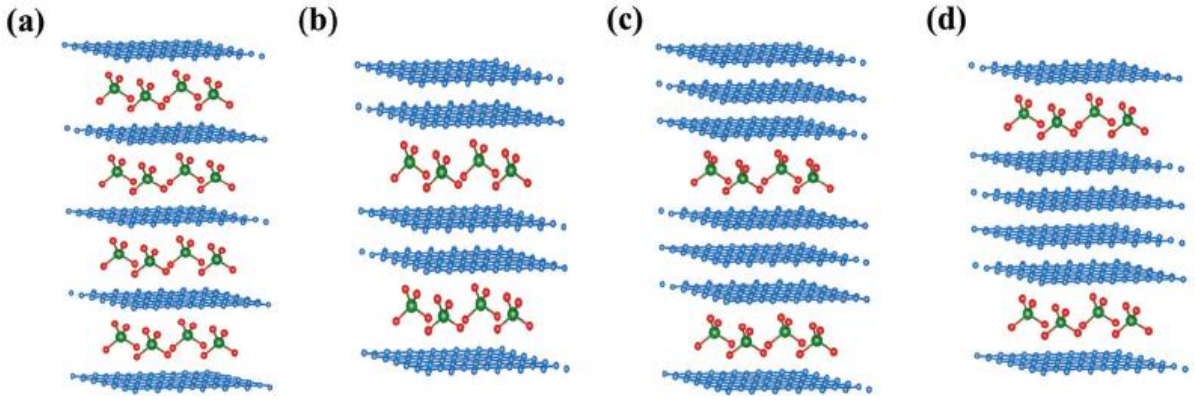
IL6

Recent progresses in the field of rechargeable ion batteries have given directions to look for alternative batteries and electrode materials that can lead toward the enhancement of battery performance. Recently an ultrafast rechargeable Al-ion battery has been reported (**Nature** *520*, 324−328, **2015**) with high charge/discharge rate, high voltage and high capacity that use a graphite-based cathode. Identifying a suitable electrode material with desirable electrochemical properties remains a primary challenge for any rechargeable ion batteries. Using the first-principles calculations, we have investigated the $AlCl_4$ intercalation mechanism (Scheme 1) into various carbon-based cathode electrodes and their ultrafast charging/discharging rate to understand the whole process. Interestingly, we show here that an anion ($AlCl_4^-$) intercalates as opposed to other Al- and Li-ion based rechargeable batteries. Ab initio molecular dynamics simulations have been performed to gain further insights in the $AlCl_4$ intercalated structures. We show here that designing of electrode materials can be very promising to improve the performance of such Al-anion based batteries.[1-3]



Scheme 1: Different $AlCl_4$ intercalation mechanisms in graphite electrode for Al-ion battery.

References:

[1] P. Bhauriyal, A. Mahata, B. Pathak, *Phys. Chem. Chem. Phys* **19** (2017) 7980.
[2] P. Bhauriyal, A. Mahata, B. Pathak, *J. Phys. Chem. C* **121** (2017) 9748.
[3] P. Bhauriyal, A. Mahata, B. Pathak, *Chemistry An Asian Journal* **12** (2017) 1944.

Computational Design of Nanomaterials for Energy and Environmental Applications

IL7

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Designing molecules and materials with desirable as well as tunable functions have been one of the primary goals of research within the scope of theoretical modeling and simulation. In the present talk, our recent research activities related to computational designing of materials with tailored properties will be briefly summarized. In particular, some of the thrust areas of materials towards energy-related research dealing with hydrogen storage and catalytic pathways for water splitting, etc. will be focused. In addition, we will also discuss the gold-based nanocatalysts towards the environmental applications; in particular, the most notable is the environmentally important reaction of combustion of CO to CO2 at temperatures far below room temperature. Thus, the application to hydrogen energy related issues of generation and storage of hydrogen as well as the environmental applications through the gold-based catalysts will form the subject matter of the talk.

Mechanism of Initiation, Association and Formation of Amyloid Fibrils Modeled with the N-terminal Peptide Fragment, IKYLEFIS, of Myoglobin G-helix

Sunita Patel[1,2*], Yellamraju U. Sasidhar[3], Kandala V. R. Chary[1,4]

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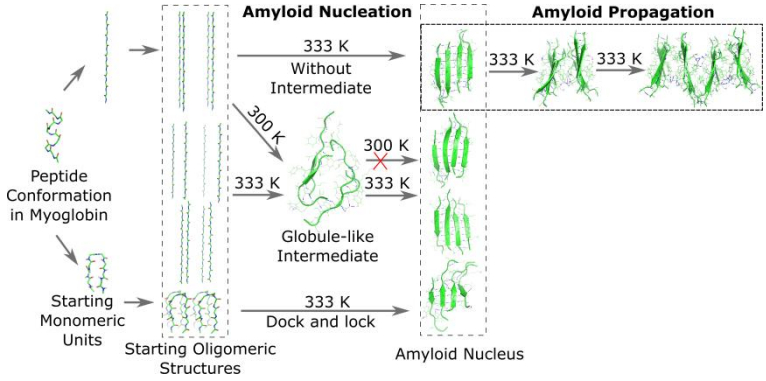
[3]*Department of Chemistry, Indian Institute of Technology Bombay, Mumbai, India*
[4]*Tata Institute of Fundamental Research, Mumbai, India*

Some peptides and proteins undergo self-aggregation under certain conditions, leading to amyloid fibrils formation, which is related to many disease conditions [1]. It is important to understand such amyloid fibrils formation to provide mechanistic detail that governs the process. A predominantly α-helical myoglobin has been reported recently to readily form amyloid fibrils at a higher temperature, like that of its G-helix segment [2]. Here, we have investigated the mechanism of amyloid fibrils formation by performing multiple long molecular dynamics simulations (27 μs) on the N-terminal segment of the G-helix of myoglobin. These simulations resulted in the formation of a single-layered tetrameric β-sheet with mixed parallel and anti-parallel β-strands and this is the most common event irrespective of many different starting structures. The single-layered tetrameric β-sheet showed a polymorphic behavior and its formation takes place following three distinctive pathways. The process of fibril initiation is dependent on temperature. Further, this study provides mechanistic insights into the formation of multi-layered fibrilar structure, which could be applicable to a wider variety of peptides or proteins to understand the amyloidogenesis.



Mechanism of amyloid fibril formation in the peptide IKYLEFIS from G-helix of the myoglobin G-helix

References:

[1] Nasica-Labouze J, Nguyen PH, Sterpone F, Berthoumieu O, Buchete NV, Coté S, De Simone A, Doig AJ, Faller P, Garcia A, Laio A, Li MS, Melchionna S, Mousseau N, Mu Y, Paravastu A, Pasquali S, Rosenman DJ, Strodel B, Tarus B, Viles JH, Zhang T, Wang C, Derreumaux P. Amyloid β Protein and Alzheimer's Disease: When Computer Simulations Complement Experimental Studies. *Chem Rev.* **2015**,115:3518.

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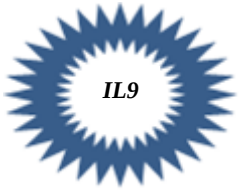
A mechanistic simulation study of the initial steps in the DNA Base Excision Repair System



Petra Imhof

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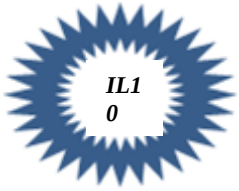
The Base excision repair (BER) system is a machinery of enzymes, recog- nising, removing, and correcting mispairs in the DNA. In the _rst step of the base excision repair system glycosylases recognise a damaged or mispaired base and remove it via glycosidic C1'-N1 bond hydrolysis. Apurinic/apyrimidinic endonuclease (APE) then cleaves the DNA backbone at the abasic site so as to allow subsequent insertion of a new, correct nucleotide by polymerase _ and ultimately sealing of the backbone by a ligase enzyme. This contribution illustrates how modelling and simulation a_orded us with insight into DNA mismatch recognition by the BER enzyme human thymine DNA glycosylase (TDG). We will furthermore present the mechanism of base excision as revealed by our simulations. Finally, the role of active-site residues in the APE-DNA complex in stabilisation of a reaction-competent complex and their function in the enzymatic DNA backbone cleavage reaction will be dis-cussed.

Temperature Accelerated Sliced Sampling: An Efficient Approach for Exploring Complex High Dimensional Free Energy Landscapes



Nisanth N. Nair

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Biased sampling of collective coordinates is a widely used strategy to accelerate rare events and compute free energy changes in molecular dynamics simulations. Computational efficiency of such methods decreases with increasing number of collective coordinates and is often limited to 2 or 3 coordinates. This severely limits the predictive power of the enhanced sampling approaches. Here we propose a new method called Temperature Accelerated Sliced Sampling (TASS) which integrates temperature acceleration with umbrella sampling and/or metadynamics sampling in a manner that a large number of orthogonal collective coordinates could be sampled simultaneously. TASS also allows one to add or remove collective coordinates perpendicular to the umbrella sampling coordinates as required. The approach allows one to perform a controlled exploration of a complex free energy landscape that is broad and unbound, like in the case of A+B type reactions, drug binding etc. After demonstrating the accuracy of our method, I will demonstrate its applications in sampling complex enzymatic reactions using QM/MM based molecular dynamics.

References:

[1] S. Awasthi, V. Kapil and Nisanth N. Nair, J. Comput. Chem. 37 1413 (2016).
[2] S. Awasthi and Nisanth N. Nair, in preparation.

En route to 'Healthy Aging' – Are we there yet?

IL1
1

Yasha Hasija

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Aging is an inevitable biological phenomenon. The tremendous rise in chronic age-related disorders (ARDs), comorbidities, and geriatric syndromes is already presenting serious challenges for countries all around the world. The major risk factors associated with ARDs include advancing age, genetic predisposition, gender, and ethnicity. While the completion of the Human Genome Project and the HapMap project has generated huge amount of data on genetic variations; Genome-Wide Association Studies (GWAS) have identified genetic variations associated with several disorders including ARDs. However, a holistic understanding of the genetic mechanisms determining susceptibility to ARDs, targeting which may lead to paradigm shift in the prediction and/or treatment of these diseases, is lacking. With this premise, we have followed a systematic systems biology approach towards understanding the biology behind ARD causation. Towards this, we have developed a computational pipeline comprising of dbAARD, database of Aging and Age Related Disorders, which hosts information on more than 3000 genetic variations significantly associated with 51 ARDs; followed by construction of a machine-learning based gene prediction tool AGP (Age Related Disorders Gene Prediction) to prioritize genes associated with ARDs. Subsequently, we designed and executed a systems biology approach to prioritize drugs that may target multiple age related disorders. Our methodology, focused on the analysis of biological pathways and protein-protein interaction networks that may contribute to the pharmacology of age related disorders, included various steps such as retrieval and analysis of data, protein-protein interaction network analysis, and statistical and comparative analysis of topological coefficients, pathway, and functional enrichment analysis, and identification of drug-target proteins. We assume that the identified molecular determinants may be prioritized for further screening as novel drug targets to cure multiple ARDs.

GSK-3β Inhibitors as Anti-Alzheimer's Agents : Computing in Chemistry Biology leading to Anti-Alzheimer Agent

IL1
2

Prasad V. Bharatam

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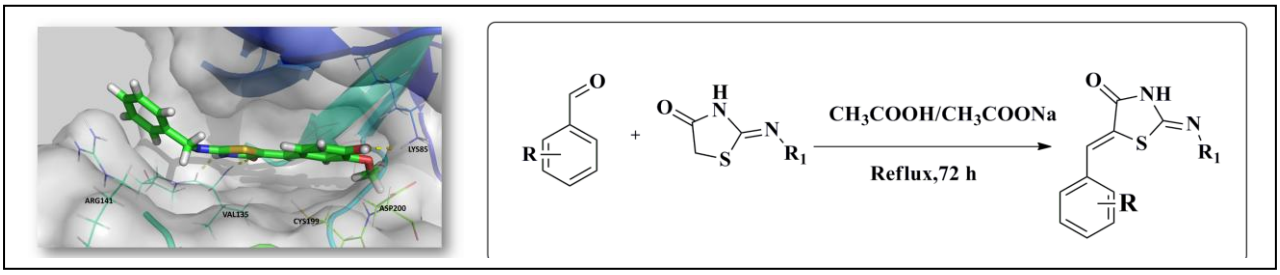
GSK-3β is an important enzyme implicated in diabetes, Alzheimer's disease, cancer and malaria. Inhibition of this enzyme can potentially solve some of the above ailments. Pharmacoinformatics methods can be successfully employed to design GSK-3β inhibitors. Molecular docking methods provide information regarding the interaction between ligands and the enzyme. QSAR methods are useful in designing new leads. Pharmacophore mapping methods are useful to perform virtual screening of compounds to identify new leads. Many other pharmacoinformatics methods can be used to perform lead optimization. Especially, molecular dynamics methods can be used to describe the stability of the inhibitor-enzyme interactions. Quantum chemical methods can be used to know the electronic details of the leads.

5-benzylidene-2-iminothiazolidin-4-one derivatives were designed using pharmacoinformatics techniques. Selectivity of these ligands was examined against CDK-2 and CDK-5. The identified compounds were then taken up for synthesis, followed by biological evaluation. The biological evaluation resulted in the identification of ten compounds to be active in lower nano molar range (2.1 to 85.4nM), in "fluorescence resonance energy transfer" biochemical assay. Out of these three have been found to selective against CDK-2.



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POSTERS

Extraterrestrial Chiral Molecules: Pathways for stereoinversion

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P1

The search for extraterrestrial chiral molecules, particularly in interstellar medium (ISM), is exciting since it can provide the much needed insights towards the origin of life on the planet Earth, which in fact is still unanswered. Towards this, we are attempting to unveil the mechanism of stereoinversion in chiral molecules likely to be present in the ISM [1]. The pathways for stereoinversion are explored under the conditions akin to the ISM, using a Global Reaction Route Mapping (GRRM) strategy. The pathways proposed may provide valuable guidance to the studies detecting the presence of chiral molecules and their related intermediates in the outer space.

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Dispersibility of carbon nanotubes in organic solvents: Do we really have predictive models?[1]

P2

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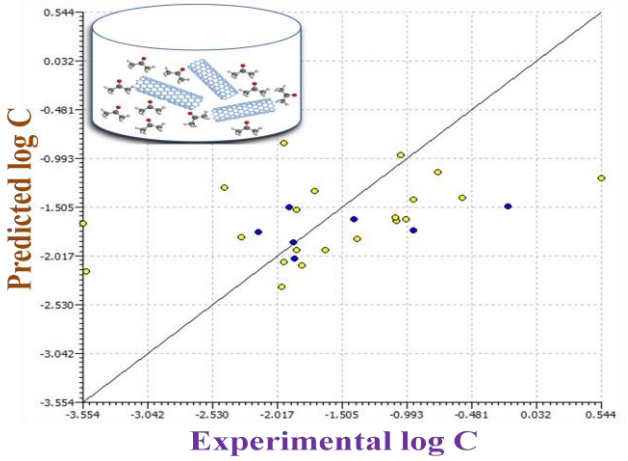
Now-a-days, quantitative models for predicting the physico-chemical properties of chemical compounds are most sought after in any environmental investigation. The real external predictability of a model, however, depends upon its ability to make successful prediction for a set of compounds never exposed to the model during its development. This work examines the real predictivity of the existing models as well as those developed using quantum chemical descriptors in the present work for the dispersibility of single-walled carbon nanotubes in a variety of organic solvents.



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Dispersion corrected density functional study of CO Oxidation on pristine/functionalized/doped graphene surfaces in aqueous phase

P3

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The catalytic oxidation of CO by molecular oxygen (O_2) over graphene, epoxy functionalized graphene and sulphur doped graphene surface is investigated theoretically by employing dispersion corrected Density Functional Theory. The adsorption of O_2 and CO molecules over the pristine, functionalized and doped graphene surface has been compared. The channel for oxidation of CO to CO_2 is elucidated in detail in the presence of aqueous solvent. Computations suggest that catalytic cycle of CO oxidation is initiated through the ER-mechanism, with the formation of a carbonate intermediate, the second pre-adsorbed CO reacts with the carbonate intermediate through LH-mechanism whereby, two CO_2 molecules are released and adsorption surface becomes available for the subsequent reaction. The activation barrier for CO oxidation is considerably lowered in the case of oxidation over functionalized 12.45kcal/mol and doped 14.52kcal/mol graphene surface in comparison to the observed barrier of 23.98kcal/mol for the pristine graphene.

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Comparative analyses of Local Spatial Stochasticity, arisen due to Polymorphic mutations in MHC I and II proteins' structure

P4

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Major Histo-comaptibility Complexes (MHCs) are the proteins which are highly polymorphic in nature.[1] Earlier studies have shown that polymorphic mutations in MHC I have different pattern of local structural perturbations than auto immune disease causing mutations.[2] In this study, we tried to compare between polymorphic mutations of MHC I and MHC II. The result from MHC I showed a significantly different (MANN Whitney U test, $P < 0.001$) pattern of local spatial stochasticity at core and surface of proteins.[2] (Figure 1)
MHC II molecules also have huge amount of polymorphic mutations. Authors are interested to study if various kinds of polymorphisms could create the same pattern of spatial stochasticty or not.

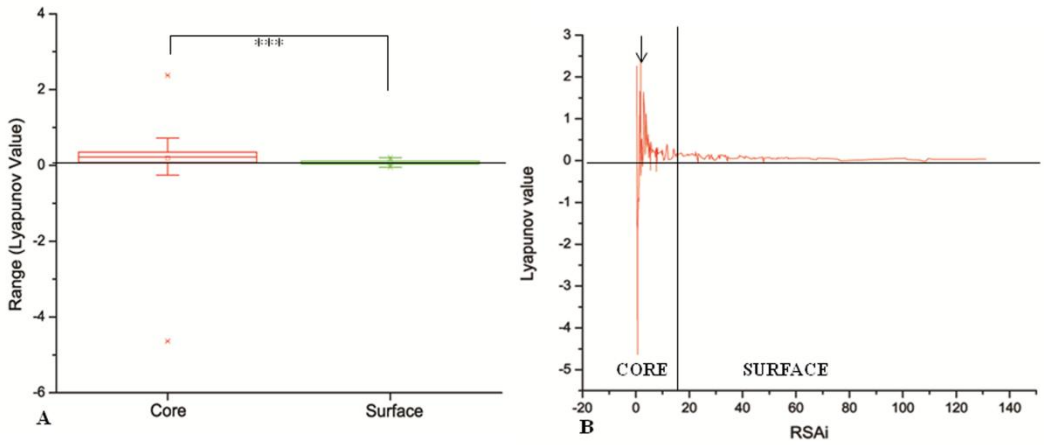

Figure1: A) Significant difference ($P < 0.001$) of Lyapunov values between core and surface of MHC I proteins due to polymorphic mutations. B) Spatial stochasticity shows core has more amount of local fluidity (+ve lyapunov value) than surface (MHC I).

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Computational studies to decipher the mechanisms of F^{334} to L/C mutation(s) associated functional collapse of PDE10A in Chorea disorder: Catalytic loss and Structural instability

P5

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The movement disorder Chorea, which is characterized by rapid loss of spiny neurons, is caused by mutations in the Phosphodiesterase 10A (PDE10A) gene. Such mutations in PDE10A, like previously known F^{334} to L mutation and recently reported F334 to C mutation, render the protein functionally inactive, finally leading to perturbation in cAMP signal transduction cascade. In this study, we have used various computational methods to decode the intricate mechanisms of mutations associated functional deregulation of PDE10A. Though F^{334} to L (Phenylalanine to Leucine) mutation does not change the chemical environment of the catalytic pocket in terms of maintaining hydrophobicity, loss of π-stacking interaction with ligand (Cytidine triphosphate, CTP) leads to higher fluctuation of ligand. This in turn results increase of torsion in ligand's rotatable bonds, causing it to spatio-temporally loose more protein contacts in all forms (H-bonds, hydrophobic interactions, ionic bonds and water bridges). However, no structural loss of protein is associated with this mutation. Structural integrity of the protein is manifested by low protein RMSD / RMSF values (comparable with wild type protein) and no loss of secondary structures during simulation time window. On the other hand, F^{334} to C (Phenylalanine to Cysteine) mutation introduces polar nature in the environment. This mutation does not alter protein-ligand interactions in the catalytic cleft, but the polar Cysteine residue introduces structural instability in the region. This is seen as higher protein RMSD and RMSF values of the catalytic core region. The ligand maintains its low rotatable bond torsions and usual protein contacts. Loss of structure in PDE10A's catalytic region accounts for destruction of catalytic activity. In summary, our studies explicitly demonstrated that different mutations in same residue of PDE10A mediate enzyme inactivation by different mechanism, namely catalytic incompatibility and structural deformation.

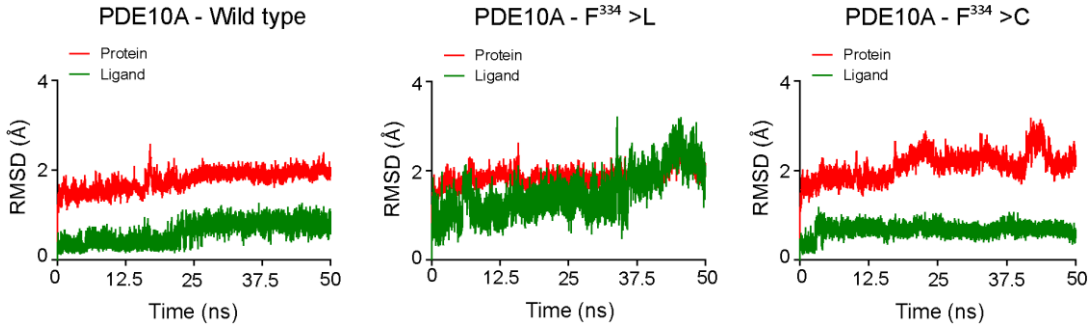

Figure: RMSD values of wild type / different mutants of PDE10A and the ligand shows that in F^{334}>L mutant the ligand is unstable with high values of RMSD. In the F^{334}>C mutant protein has higher RMSD values accounting for its instability.

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Computational Investigation on Fe(IV)–Oxo–Hydroxo Oxidant Mediated Intramolecular Ligand Hydroxylation and Role of Lewis Acid on O−O Bond Cleavage

P6

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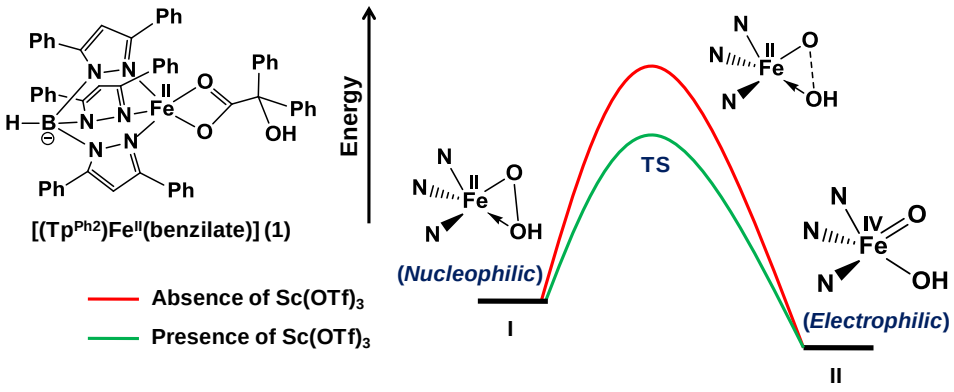
Over the last decades, biomimetic oxidation of alkanes and alkenes by iron complexes in the presence of "ready oxidant" H2O2 has been extensively studied. Several iron–oxygen intermediates such as iron(III)–(hydro)peroxo and iron(IV)–oxo species have been generated through reduction of dioxygen by iron(II) complexes. However, the selective oxidation of C–H and C=C bonds by biomimetic complexes using O2 are rare and remains a major challenge. In this endeavour, a nucleophilic side-on FeII–hydroperoxo oxidant (I) is proposed to form in the reaction of high-spin iron(II) complex [(TpPh2)FeII(benzilate)] (1) [TpPh2=hydrotris(3,5-diphenylpyrazolyl)borate] with dioxygen in benzene at ambient temperature.[1] The concomitant decarboxylation of benzilic acid yields benzophenone. I undergoes O−O bond cleavage to generate an electrophilic FeIV–oxo–hydroxo oxidant (II). The dissociation of O−O bond is facilitated in the presence of a Lewis acid e.g. Sc(OTf)3.[2] In the absence of any substrate, the oxidant intramolecularly hydroxylates one of the phenyl rings at ortho position on the TpPh2 ligand. We have performed DFT calculations to investigate the energetics of the O−O bond cleavage of FeII–hydroperoxo species prior to the generation of electrophilic oxidant both in the absence and presence of Sc(OTf)3. Emphasis is placed on detailed mechanistic investigation of the intramolecular ligand hydroxylation mediated by both nucleophilic and electrophilic oxidant to unfold the real oxidant responsible for this transformation. Additionally, hydroxylation of strong C−H bond in cyclohexane by II is also explored.



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DFT Investigation on the Mechanistic Study of Olefin Isomerization Reaction by Dimeric Palladium(I) Catalyst

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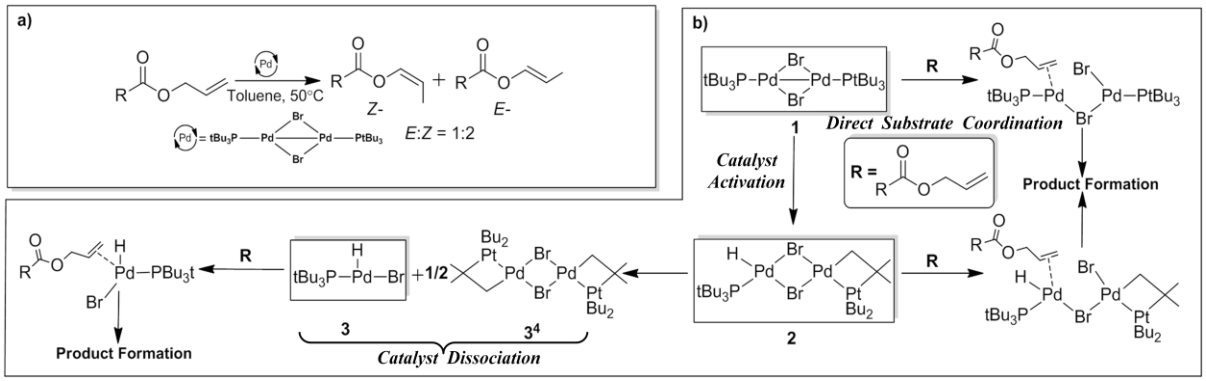
P7

Enol esters and their derivatives are considered as one of the most valuable precursors in a variety of organic transformations[1]. Due to their importance in organic transformations and pharmaceutical chemistry, several studies have been performed towards the development of enol ester synthesis[2]. Recently, Gooβen et. al.[3] have developed an olefin isomerization reaction for the formation of enol esters with the help of highly active dimeric $[Pd(\mu\text{-}Br)(P^tBu_3)]_2$ catalyst 1 (Scheme 1a). Preliminary DFT calculations have been performed to address the actual catalyst responsible for the transformation with successive effort in understanding the detailed mechanistic profiles of the title reaction. We have considered the direct coordination of the substrate (R) to the dimeric complex 1 as well as the activation of catalyst 1 via internal C-H activation will furnish dimeric Palladium(I)-hydride species 2 (Scheme 1b). Unfortunately, both the pathways show unfavourable thermodynamics which is incompatible with the experimental conditions. Additionally, the generation of the monomeric Palladium(II)-hydride species 3 via the different possible decomposition route is taken into consideration (Scheme 1b). Our computational endeavour suggest that 3 will act as a potential candidate for the facile conversion of allylic ester to enol ester. In addition, the active catalyst formation is found to be the rate-limiting step of the overall reaction.



Scheme 1 (a) Isomerization of allylic esters to enol esters. (b) Mechanistic routes for the catalytic transformation.

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Synthesis and Investigation of New different Imidazole [1, 2-*c*] Thieno [3, 2-*e*] Pyrimidine Derivatives as Potent Antimicrobial Activity

P8

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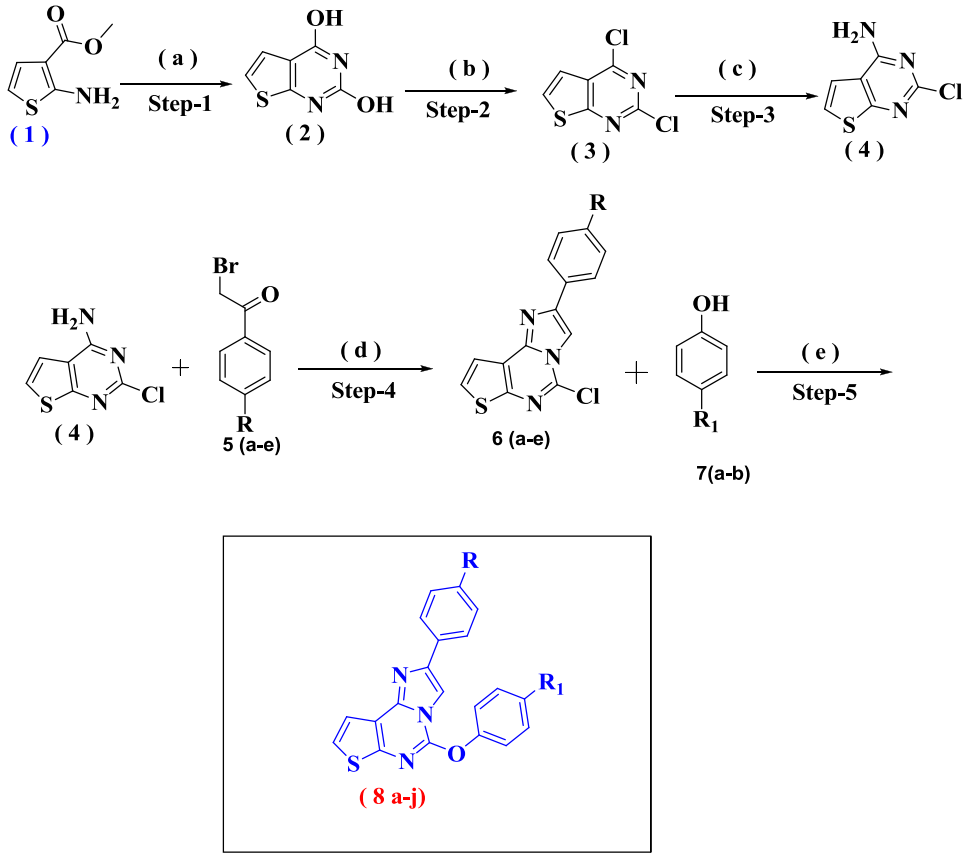
A series of Imidazolo[1, 2-*c*] Thieno [3, 2-*e*] Pyrimidine derivatives (8 a-i) were synthesised from 2-chlorothieno[2,3-*d*]pyrimidin-4-amine (4) and aromatic phenacyl bromides (5 a-e) in Ethanol at reflux temperature. The synthesised compounds were characterized on the basis of their spectral (IR, ^{1}H NMR, ^{13}C NMR, Mass) data and screened for antimicrobial activity where compounds 8h, 8j showed significant activity.

SYNTHETIC SCHEME I



Reagents and Reaction conditions: **(a)** Urea, 200^{O}C, 3 hrs(b) $POCl_3$, DMF(cat), Reflux, 6 hrs (c) Aqueous Ammonia, Na_2CO_3, THF,0^{O}C-RT, 3 hrs. (d) Ethanol, $NaHCO_3$, Reflux, 3-4 hrs.(e) Copper powder,Cs_2CO_3,DMF, 100°C; 60 watts (microwave irradiation).

Hydrogen Loading Efficiency of Sc Decorated Octamethylcalix[4]arene and Calix[4]arene

P9

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The increasing energy demand and limited supply of fossil fuels, their adverse effect on environment require the need for clean and sustainable energy source. Hydrogen is a potential energy source due to its renewable, light weight, highly abundant, highest energy density per unit mass and produce water when used in fuel cells.[1,2] Hydrogen storage is the major problem in achieving this goal.

In the present study, Octamethylcalix[4]arene (MeCX) and Calix[4]arene (CX) is decorated with Sc metal and their hydrogen storage capacity have been investigated by computational methods. By applying density functional theory all the geometries are optimized by M06 method with 6-311G(d,p) and their structural stability have been analyzed. It is observed that Sc decorated MeCX and CX improves their average binding energy with hydrogen molecules. Sc atoms strongly coordinate with benzene rings of MeCX and CX through Dewar coordination while Sc metal adsorb hydrogen molecules by Kubas mechanism. On saturation with hydrogen, each Sc atom traps 4 H_2 molecules on both MeCX and CX. The low value of sequential H_2 adsorption and desorption energy for physisorbed H_2 molecules show the high reversibility of H_2 in both the systems. Molecular dynamics simulations of both the hydrogen trapped Sc decorated MeCX and CX systems, show that these systems are stable up to 273 K. The hydrogen storage capacity of Sc decorated MeCX system is found to be 9.7 wt % and for CX system 8.9 wt %. The energetic and storage capacity meets the DOE target which makes them a propitious hydrogen storage material.

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RNA secondary structure analysis of the 5′ UTR of the Flavivirus genomic RNA

P10

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Positive sense, single stranded genomic RNA containing flaviviruses belonging to the family *flaviviridae* have been broadly classified into mosquito borne (MBFV), tick borne (TBFV), no known vector (NKFV), and insect specific (ISFV) classes. Many of these viruses are responsible for life threatening diseases in humans, for example Dengue (DENV), Zika (ZIKV), and tick born encephalitis virus (TBEV). It is well known that the untranslated regions of the genomic RNA play an important role in the life cycle of flaviviruses [1]. Recent efforts in combating flaviviruses are aimed at designing RNA based aptamers to target these UTR regions [2]. In case of Dengue, the most well studied flavivirus, it has been reported that differences in the sequence and the corresponding secondary structures the 5′ UTR, besides changes in the E protein, may underpin the differences in the severity of the disease caused by different genotypes [3]. A comparative study of predicted RNA secondary structures of few select viruses has shown that the unrelated flaviviruses did show similar RNA structural architecture in the 5′ UTR region [1]. Here, we present a global survey of the RNA secondary structural architecture of the critical 5′ UTR of the flaviviral genomic RNA. Complete genomes of flaviviruses deposited in the NCBI are used in the current study. The 5′ UTR sequences are subjected to RNA secondary structure prediction using the default parameters in mFOLD [4]. The resulting structures are compared within a virus (e.g. DENV serotypes 1-4), across different groups in a class (e.g. DENV vs. YF group of MBFV), and finally across the classes (e.g. MBFV vs. TBFV). There are marked differences in the RNA structural architecture within groups and across the classes of flaviviruses. The predicted RNA secondary structures revealed similar architecture among the flaviviruses affecting humans, irrespective of the vector, except for West Nile and Kunjin virus belonging to the JEV group of MBFV. And also viruses with different dead-end hosts have shown different structural architecture of the 5′ UTR region, implying a possible correlation between the RNA secondary structure and host selection. We have also observed that viruses belonging to NKV class share similar 5′ UTR structure as DENV. The observed RNA structural elements that are unique to the virus and are unique among a class/group of viruses may be exploited as possible biomarkers for further developments in both diagnostics as well as RNA based aptamer design.

References:

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QSAR and Molecular Docking Analysis of synthetic compounds against Breast Cancer Targets

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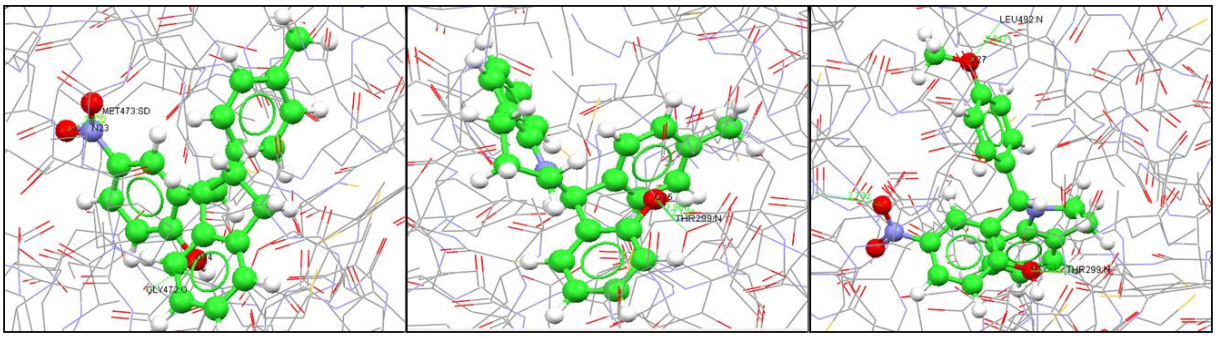
P11

Breast cancer is the most frequently diagnosed cancer among women and the leading cause of cancer death worldwide. Studies have already proved that the Indoline, Morpholine and phenolic compounds N-(2-hydroxy-5-nitrophenyl(40-methylphenyl)methyl)indoline, 2-((3,4-dihydroquinolin-1(2H)-yl)(p-tolyl)methyl)phenol and 2-((1,2,3,4-tetrahydroquinolin-1-yl)(4-methoxyphenyl)methyl)phenol exhibit effective cytotoxic activity against breast cancer cell lines. The different Indoline, Morpholine and phenolic derivatives were subjected to QSAR analysis with an attempt to derive and understand the relationship between the biological activity and molecular descriptors by multiple regression analysis. The investigation was conducted to look for the common structural features between the derivatives which donate to a good biological activity. A set of 100 derivatives with their IC_{50}values were considered for the study. The model generated gave a good correlation value of 0.920 and 0.995 for the training and the test sets respectively. Molecular docking analysis of the five targets Progesterone Receptor (PR),Estrogen Receptor (ER), Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase (PTEN), Receptor tyrosine-protein kinase erbB-2 (ERBB2) and Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (PIK3CA) responsible for breast cancer with the compounds N-(2-hydroxy-5-nitrophenyl(40-methylphenyl)methyl)indoline, 2-((3,4-dihydroquinolin-1(2H)-yl)(p-tolyl)methyl)phenol and 2-((1,2,3,4-tetrahydroquinolin-1-yl)(4-methoxyphenyl)methyl)phenol were performed. The results indicate that 2-((3,4-dihydroquinolin-1(2H)-yl)(p-tolyl)methyl)phenol has a potential inhibitory activity against all the targets. This study shall help in rational drug design and synthesis of new selective anticancer inhibitors with predetermined affinity and activity.



ESTROGEN with N-(2-hydroxy-5-nitrophenyl(40-methylphenyl)methyl)indoline

ESTROGEN with 2-((1,2,3,4-tetrahydroquinolin-1-yl)(4-methoxyphenyl)methyl)phenol

ESTROGEN with 2-((3,4-dihydroquinolin-1(2H)-yl)(p-tolyl)methyl)phenol

Protein-Ligand docking by GOLD and Active Sites of Estrogen Receptor with synthetic compounds

Computational Investigation on Conversion of Thiuram Monosulfides to Disulfides

P12

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In presence of visible light, thiruam monosulfides get converted to corresponding disulfides. A well studied case has been of a topical drug, monosulfiram (tetraethylthiuram sulfide) (MS) used in the treatment of scabies. It gets converted into disulfiram (tetraethylthiuram disulfide) (DS), which is used in the treatment of alcohol aversion therapy. In the present investigation an *in silico* study is carried out to explore the mechanism of conversion of MS into DS. Structures and energetics of MS and DS are obtained at the MP2 and DFT level of theory. Their reactivities are assessed in terms of conceptual Density Functional Theory (CDFT) based reactivity descriptors. Bond dissociation energies of the targeted molecules are also determined. Lowest singlet excited states of MS and DS along with their potential energy surfaces are computed. It is found that conversion of MS into DS occurs in both thermal and photochemical situations.

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Mechanism of Telomerase Catalyzed DNA Polymerization: A QM/MM Molecular Dynamics Study

P13

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Telomerase which is involved in the incorporation of telomeric DNA sequence at the 3' end of eukaryotic chromosome, has particularly gained interest in the anti–cancer therapeutic research because of their hyperactivity found in cancer cells. The molecular mechanism of telomerase catalyzed nucleic acid polymerization, especially the general base in deprotonation of 3'-hydroxyl, is not known yet. To shed light on this, we perform extensive DFT based QM/MM molecular dynamics (MD) simulation combined with powerful enhanced sampling technique, namely metadynamics, based on which, we present here a novel mechanistic insight into the telomerase catalyzed DNA polymerization, in particular the role of bulk water in deprotonation of 3'-hydroxyl will be discussed. We will also show that our findings are in agreement with the results from timeresolved X-ray crystallography and the kinetic experiments.

Structural and functional characterization of PE1 and PE2 proteins in *Mycobacterium tuberculosis*

P14

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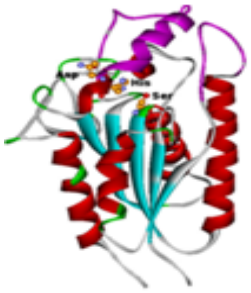
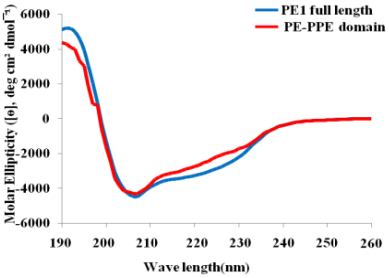
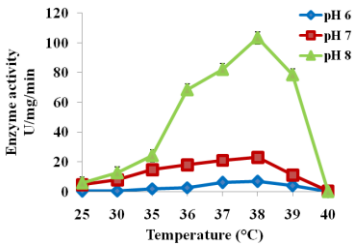
Tuberculosis is mainly caused by *Mycobacterium tuberculosis* (*M.tb*). The PE and PPE proteins first reported in the genome sequence of *M.tb* H37Rv strain are now identified in all mycobacterial species. The functional roles of these superfamily members need to be explored. The PE-PPE domain (Pfam ID: PF08237) is a 225 amino acid residue conserved region located towards the C-terminus of some PE and PPE proteins. This domain comprises a pentapeptide sequence motif GxSxG/S at the N-terminus and conserved amino acid residues Ser, Asp and His that constitute a catalytic triad characteristic of lipase, esterase and cutinase activities. The fold prediction and 3D structure modeling of the PE-PPE domain revealed a serine α/β- hydrolase fold with a central β-sheet flanked by α-helices on either side. These results provide directions for the design of experiments to establish the function of PE and PPE proteins. The characterization of the probable operonic ORFs Rv0151c (*pe1*) and Rv0152c (*pe2*), revealed that both genes are co-transcribed. PE1 and PE2 proteins demonstrated esterase activity and hydrolyzed short to medium chain *p*-nitro phenyl esters with more specific activity for *p*-nitro phenyl caproate (C6) with the optimal catalytic conditions at 37-38°C and pH 7.0-8.0. The esterase activity of the full length PE1, PE2 and their PE-PPE (α/β- serine hydrolase) domains are similar indicating that the functions of PE-PPE domains are independent of the full length proteins. The esterase activity was further confirmed using serine protease inhibitor; PMSF. The mutant proteins (PE1 Ser246 to Ala and PE2 Ser163 to Ala) did not possess biochemical activities. The thermal denaturation temperature of PE1 and PE2 proteins were found to be 50°C. With these experiments, we conclusively show that PE1 and PE2 of *M.tb* belong to esterase family of enzymes.



Overall fold of PE1, PE2



CD spectra of PE1 and its PE-PPE domain



Effect of pH and temperature on PE1

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Interplay of Sequence Variation, Hydration Effects and Conformational Propensity Within Biologically Relevant Long Double Stranded DNA Sequences

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The factors underlying coupling of the physico-chemical environment of gene-length DNA sequences with their conformational propensities, and thereby their ability to appropriately perform their biological functions, remain poorly understood. In case of short DNA double strands, it has been shown that surface dehydration brings about higher relative stability of the A-form of the DNA, whereas the canonical B-form is the most stable conformation in fully aqueous environment[1]. Experiments suggest that polar amino acids mostly interact with B-nucleotides, while hydrophobic amino acids interact extensively with A-nucleotides[2]. Importantly, the B-to-A transition could lead to wider and more flattened out minor groove, which in turn should allow more space for interactions with hydrophobic side chains of protein[3]. Thus, modulations in DNA conformational propensities are likely to manifest in biological phenomena that involve protein mediated processes such as gene expression and regulation.

In the present study, we attempt to address how alterations in gene sequences bring about subtle changes in the hydration propensities of double stranded, 100 base pair DNA strands. Beginning with pure AT sequences in the canonical B- and A- conformations, we introduce periodic heterogeneities until the pure GC strand is reached, thus altering local base pair hydrogen bonding and rigidity. Fully atomistic molecular dynamics (MD) simulations are exploited to investigate the dynamic changes in sugar puckering modes on the sugar-phosphate backbone (C3'-endo for A-forms and C2'-endo for B-forms), backbone torsion angles and other parameters including solvent radial distribution function and density profile to distinguish conformational differences as a function of base pair heterogeneity. The dimensions of the major and minor groove, as well as local differences in solvent dynamical relaxation are further investigated. Ongoing work pertains to estimating the solvation free energy components along the 5' to the 3' end for the sequences, with attempts to correlate them with local (A / B) conformational propensities. Armed with these results, future directions will involve probing the differential binding of the heterogeneous 100 base pair sequences with suitable protein substrates.

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Chemical Reactivity Parameters of Peptide Nucleic Acid Stacks

P16

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Peptide Nucleic Acids (PNAs) the achiral DNA mimics with amide backbone are emerging as attractive leads for drug development through antisense approach [1]. Due to its ability to bind complementary DNA and RNA with high affinity, great specificity and high resistant against protease and nucleases, it acts as a prerequisite for successful antisense applications [2]. Here, we have analyzed the quantum chemical descriptors of the GC, AT and AU PNA constructs. Such a study is of importance that further enunciates their role in anticancer activities [3]. The construction of PNA stacks are made through the inclusion of N-(2-aminoethyl)-glycine unit at the backbone of GC-GC in fig.1, AT-AT, and AU-AU nucleic acids respectively. All the structures are optimized at B3LYP/6-31G* level of theory and found to be minima on the potential energy surface. To understand the reactivity of the molecules, ionization potential (IP), electron Affinity (EA), chemical Hardness (η), chemical Softness (S), chemical potential (μ) and HOMO-LUMO gap (E_g) and binding energy have been calculated. From the value of chemical potential, it was found that AU stack is the most reactive and is prone for electrophilic attack that is confirmed from large electronegativity value when compared with GC and AT stacks. In addition, from the frontier molecular orbital analysis, it is observed that the HOMO's are localized in the purine site suitable for nucleophilic attack and the LUMO electron density is localized in the pyrimidine site for GC and AT stacks. The LUMO orbitals extend to the PNA chain in AU stack thus making it more reactive than GC and AT stacks. Hence this study suggests that the stacks containing pyrimidine bases with extended LUMO on their peptide backbone may have potential applications toward anticancer activities.

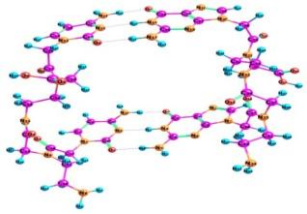

Fig.1 Optimized structure of $G_{PNA}C_{PNA}$-$G_{PNA}C_{PNA}$ at B3LYP/6-31G* level of theory.

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Excited Electronic Properties of Sn Metalloporphyrin for DSSC Applications

P17

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Organic based dyes have attracted a great deal of attention in recent days for dye sensitized solar cells (DSSC) applications as photosensitizers[1, 2]. Among the various organic dyes present, metalloporphyrins are the most commonly used chromophores as they show strong absorption bands in the visible region and also for their natural light harvesting properties[3] . This study explores the electronic transitions of SnTP molecules namely SnTP and X'SnXTPyP (absence of pyridine H), SnTPH, and X'SnXTPyHP (presence of pyridine H) for axial ligands X' = X = OH^- using TDDFT technique optimized at HF/LANL2MB level of theory. The optimized geometries were later used in calculating single point energies at B3LYP/SDD level of theory in vacuum with the C-PCM model using Gaussian 09. The excitation energies are obtained for 20 singlet states and it is observed that the absorption bands are located in the visible and near UV region signifying π- π* transitions that determines the photo-to-current conversion. Also the presence of pyridine H and the axial ligands have an effect on the excitation property of Sn metalloporphyrin. The SnTP structures without axial ligands show a wider absorption spectrum than the structures with axial ligands. As the absorption bands of SnTPH (Fig) are closer to infrared region, this molecule might result in higher photo-to-current efficiency.

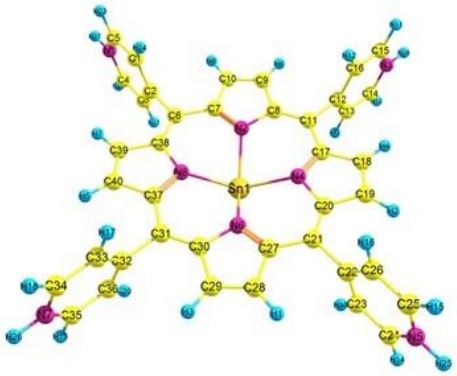

Fig: Structure of SnTPH molecule

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Molecular basis for drug resistance of CRF01_AE HIV-1 protease mutants against nelfinavir and indinavir: Molecular dynamics simulations and binding free energy calculations.

P18

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HIV-1 protease plays a crucial role in viral replication and maturation, which makes it one of the most attractive targets for anti-retroviral therapy. The majority of HIV infections in developing countries are due to non-B subtype. Subtype AE is spreading rapidly and infecting huge population worldwide. The mutations in the active site of subtype AE directly impair the interactions with the inhibitor and the non-active site mutations influence the binding of the inhibitor indirectly. The resistance mechanism of these active site and non-active site mutations is not well understood and it is important to design new effective inhibitors that combat drug resistance in subtype AE-protease. In this work, we examined the effect of non active site mutations L10F, L10F/N88S and L90M with nelfinavir and active site mutation V82F with indinavir using molecular dynamics simulation and binding free energy calculations. The simulations suggested that the L10F and L10F/N88S mutants decrease the binding affinity of nelfinavir, whereas the L90M mutant increases the binding affinity due to favourable enthalpy and entropic contributions. The loss in binding affinity of IDV in V82F mutant is due to decrease in van der Waals interaction, electrostatic and non-polar solvation energy contribution. The finding from the study revealed that when L10F co-occurs with N88S, an intramolecular hydrogen bond network is altered thus impairing the interaction of NFV. The simulations of V82F mutation with indinavir suggested changes in the conformation of P1 loop region leading to loss in hydrogen bond and hydrophobic interactions in the active site cavity. Our present study shed light on the resistance mechanism of the active and non-active site mutation observed experimentally in AE subtype.

Key words: HIV-1 protease; Nelfinavir; Indinavir; Subtype AE; Resistance mechanism

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Drug - Disease Network model: A drug repurposing strategy for Ischemic stroke

P19

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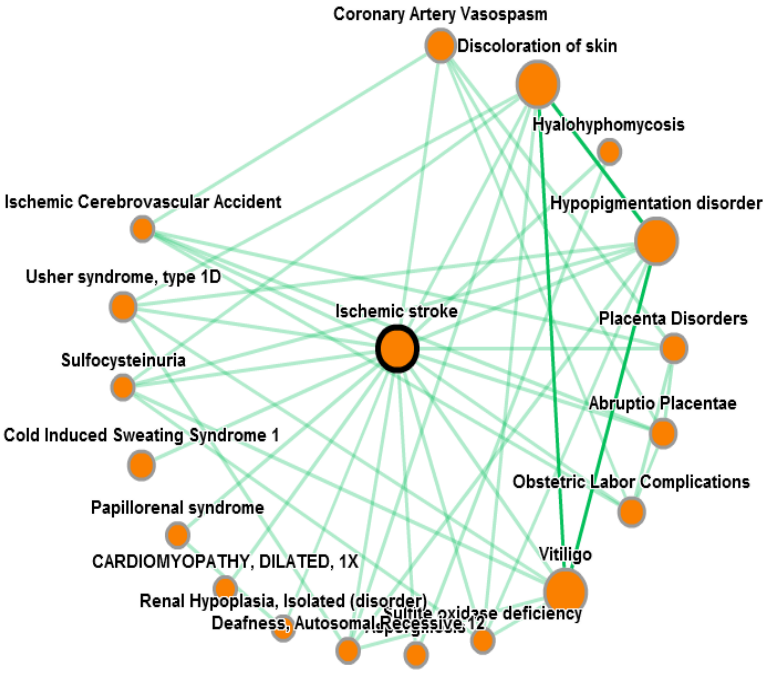
Ischemic stroke, a disease of complex nature is one of the most severe neurological disorders affecting millions of people worldwide. The therapeutic choice for cerebral ischemia is limited to only a single pharmaceutical agent, effective within a tiny time window. One of the emerging trends in the drug discovery field is to develop new use for an existing drug, a process known as Drug Repurposing.

The study was performed with the aim to identify a potential drug candidate for ischemic stroke via network based drug repositioning technique. A disease-disease interaction network model was constructed as a starting point, in order to build a complex drug-disease network. Microarray data were used in order to create the initial network model which provides a clear view of the interaction between ischemic stroke and other diseases notably, cardiovascular disease. The FDA approved drugs for the interacting diseases were taken to build a drug-disease network. Statistical tools were used to prioritize the potential candidate for ischemic stroke.



Disease-Disease Network model of Ischemic stroke

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Solubility of Methylated Nucleobases in Hydrated Ionic Liquids

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P20

Nucleobases are the nitrogen-containing hetero-aromatic molecules, which are the basic constituents of DNA. They form a variety of non-bonded interactions like electrostatic, Van der Waals, hydrophobic and π-π stacking. They are used in variety of applications such as molecular therapeutics, bio-mimetics, as coordination polymers, and in electronics and photonics [1]. They are also utilized in the agricultural and chemical industries as well. Uracil and its derivatives used as anticancer and antiviral drugs [2]. Even though their applications are vast, they are poorly soluble in water. Ionic liquids (ILs) composed of organic cations and organic, inorganic anions with a unique molecular structure, which consists both charged as well as hydrophobic domains, become popular due to their exceptional solvation abilities. A phenomenal increase in the solubility of nucleobases in ionic liquids was observed in previous studies relative to water [3]. It is important to understand the thermodynamics and solvation mechanism of these molecules in pure and hydrated ionic liquids to improve and tune their solubility.

In this study, we have calculated the solvation free energy of methylated nucleobases in pure and hydrated 1-ethyl, 3-methyl imidazolium acetate ([Emim][Ac]) ionic liquid and pure water using molecular dynamics simulations. Multi-state Bennett's Acceptance ratio (MBAR) method was used. Solvation free energies calculated in the pure water for methylated nucleobases were compared with the previous experimental and theoretical values and found to be in agreement. We observed that the solvation free energy of methylated nucleobases is more in the pure ionic liquid when compared to the pure water and increasing the mole fraction of water in the ionic liquid the solvation free energy decreased gradually. Coulombic and Van der Waals contribution to the solvation free energy calculated. To explain the solvation mechanism, we calculated radial distribution functions (RDF), spatial distribution functions (SDF) and stacking angle distribution of Emim cations to the nucleobases. From RDFs and SDFs, we found acetate anions of the ionic liquid are forming a strong hydrogen bond with the amine hydrogen atoms of the nucleobases. These hydrogen bonds contribute to the major part of the coulombic contribution to the solvation free energy. Stacking of cations to the nucleobases is the major part of the Van der Waals contribution to the solvation free energy.

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In-silico analysis of probable mutations affecting structure of isocitrate lyase in *Mycobacterium tuberculosis* and their impact on drug binding

P21

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The emergence of multidrug-resistant strains of Mycobacterium tuberculosis (Mtb) has efforts to discover novel drugs for tuberculosis (TB) treatment. Targeting the persistent state of Mtb, a condition in which Mtb is resistant to conventional drug therapies, is of particular interest. Persistent bacterial population relies on metabolic pathways that become active in low nutrient environment like glyoxylate shunt. Since the glyoxylate shunt enzymes are not present in mammals, they make attractive drug targets. This study is focused on Isocitrate Lyase (ICL), one of the enzymes in the glyoxylate shunt. This study is about the role that mutations play in the drug-protein interactions by taking *icl* protein of *Mycobacterium tuberculosis* as the putative drug target. The mutation analysis provides us information about what would be the effect of mutations which may cause drug resistance. Computational approach was used for characterizing, and molecular docking of proteins and their subsequent substrates or inhibitors.

Crystal structure of icl (pdb id-1F61) & 3- nitropropionate, and 3-bromopyruvate inhibitors was used to study the probable mutations in the *icl* protein and their effect on binding of the ligands. Molecular docking of all wild & mutated protein (ICL) with inhibitors was performed. The binding energy and inhibitory concentration was observed.

On the basis of this study, the best protein molecule residue having the lowest binding energy and Inhibition constant (Ki) was identified. The best molecule identified was further evaluated by molecular dynamics simulation of protein-ligand complex in water solvent model. The rmsd close to 2 A◦ shows the stability of the complex. Hence. the effect of mutation on the conformation, stability, functioning of *Icl* protein have been identified and characterized for further development into effective drugs which can interact and inhibit this protein even after the incorporation of point or dual mutations by natural or man-made causes.

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Molecular properties of Amino acid based Ionic Liquid in Gas and Solvent phase

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P22

Amino acid based ionic liquids (AAILs) are among the most interesting green solvents that are used as reaction and extraction solvents[1] and as electrolyte materials in batteries. They are also been explored as candid materials in separation techniques[2] and carbon dioxide capture mechanisms. Hence, we explore the molecular properties of the AAILs by choosing natural aliphatic and aromatic amino[3] acids like alanine, leucine, isoleucine, valine, methionine and phenylalanine, tyrosine, and tryptophan respectively as anions and EMIM and BMIM as cations. For this the theoretical investigation of the cation-anion interactions, nature of bonding, chemical hardness and polarisability of ionic pairs is obtained from gas phase as well as in solvents with increasing dielectric constant like, Dimethyl sulfoxide (DMSO), water, and Formamide. EMIM and BMIM interact with all the amino acids through N-H···O and C-H···O hydrogen bonds. Atoms in Molecule (AIM) analysis shows that stronger hydrogen bonds are formed in gas phase rather than the solvent medium. Chemical hardness values of aliphatic amino acid ionic liquids show a considerable increase than aromatic AAILs in solvent phase. Polarisability[4] values of the EMIM and BMIM ion pair's increases with increase in dielectric constant of solvents due to the aromatic groups present in the anion. Besides the cation chain length also increases the polarizability of the molecule in both gas and solvent phase.

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Molecular activation of RhlR by autoinducer ligand butyryl homoserin lactone in *Pseudomonas aeruginosa*: a molecular dynamics approach

P23

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In the family of opportunistic organisms, *Pseudomonas aeruginosa* is a potential one. It has the ability to infect the immunologically challenged people, like the patients of cancer, AIDS, cystic fibrosis etc. It can produce different virulence factors and among them hydrogen cyanide (HCN) is the most important one. The synthesis of HCN is mediated by an enzyme named HCN synthase. This enzyme is encoded by hcnABC operon, which is regulated mainly by three transcription factors RhlR, ANR, and LasR. These three transcription factors directly regulate the transcription of the hcnABC genes in a cluster. The RhlR protein operates as a dimer. Dimerization of RhlR protein needs the activation of the RhlR monomer by an autoinducer ligand, butyryl homoserine lactone (BHL). RhlR has two distinct functional domains, the N-terminal ligand binding domain, and C-terminal DNA binding domain. The ligand binds into the ligand binding pocket, which is present in the N-terminal domain. Here in this study we are trying to find out the impact of the BHL in the activation of RhlR using molecular dynamics approach. We have studied the behavior of RhlR monomer in presence and absence of autoinducer ligand, BHL. The exploration of this activation mechanism of RhlR protein can help researcher to develop some new drugs to block this activation pathway.

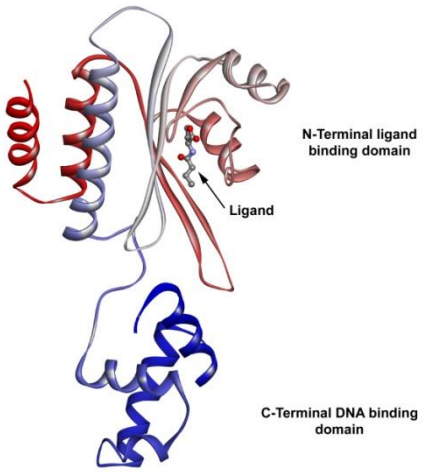

Figure: Monomer of RhlR protein, bound with autoinducer ligand, butyryl homoserine lactone.

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Complement Component fragment 5a Receptor (C5aR): Insight into Structure, Ligand Sensing and Mechanism of Activation.

P24

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Complement fragment 5a (^{h}C5a) is one of the most potent glycoprotein produced during activation of the complement system. ^{h}C5a exerts its pleiotropic effects by binding to C5aR, one of the two chemoattractant receptors of Rhodopsin family. The protein-protein interaction between ^{h}C5a and C5aR is known to contribute toward pathogenesis of several inflammatory and non-inflammatory diseases.[1] Interestingly the binding of ^{h}C5a to C5aR and its role in activation of C5aR is not well understood, due to lack of substantial structural information. Nevertheless, a plausible "two-site" binding interactions between ^{h}C5a and C5aR have been hypothesized based on biochemical studies, involving "site1" at the N-terminus and "site2" at the interhelical crevice of C5aR. To overcome the structural bottleneck, we recently illustrated a set of model structures of C5aR,[2] both in agonist free and bound state by recruiting a rational computational biology approach. In strong agreement with the reported experimental studies, the structurally unique model structure of C5aR subsequently demonstrated the orthosteric "site2" at the extracellular surface (ECS) of C5aR, in contrast to the previously hypothesized interhelical crevice of C5aR.[3] Moving ahead, we also deciphered the "site1" on C5aR at an atomistic clarity, which enabled us to generate the first ever structural complex of C5aR interacting with the native agonist ^{h}C5a and engineered antagonist ^{h}C5a-A8.[4] The study provided important insights into the activation mechanism of C5aR, demonstrating the "two-site" binding paradigm, as exemplified in few other known protein binding GPCRs. In the absence of experimental structural complexes, the set of studies provide the necessary platform for further generating the "^{h}C5a-C5aR-G protein" signaling complex, which will surely help in further understanding the pharmacology of C5aR. In summary, our model structural complexes of C5aR emerge as an excellent platform for design and discovery of potential therapeutic candidates targeting the ^{h}C5a-C5aR signaling axes.

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Estimating strengths of individual hydrogen bonds in RNA base pairs: Towards a consensus between different computational approaches

P25

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Non-coding RNA molecules are composed of a large variety of non-canonical base pairs that shape up their functionally competent folded structures. Each base pair is composed of at least two inter-base hydrogen bonds (H-bonds). It is expected that, the characteristic geometry and stability of different noncanonical base pairs are determined collectively by the properties of these inter-base H-bonds. With the development of computational capacities, numerous theoretical approaches have been implemented to study the properties of the individual H-bonds in base pairing systems. Different theoretical approaches have their respective advantages and limitations, and a consensus between them is lacking in the current literature. Here we have studied the ground state electronic properties (using DFT and DFT-D3 based methods) of all the 118 natural base pairs and 36 modified base pairs that occur in a nonredundant set of high resolution RNA crystal structures and belonging to 12 different geometric families (*cis* and *trans* of WW, WH, HH, WS, HS and SS). For all the base pairs we have calculated the H-bonding energies (E_{HB}) of individual inter-base H-bonds from their vibrational spectra obtained from Hessian calculations. We are able to overcome some of the limitations of the earlier approaches and provide a comprehensive picture regarding the average energies of different types of inter-base H-bonds. We have characterized each inter-base H-bond by 13 different parameters that describe its geometry, charge distribution at its bond critical point (BCP) and $n\rightarrow\sigma^*$ type charge transfer between filled π orbital of the H-bond acceptor to the empty anti-bonding orbital of the H-bond donor. On the basis of the extent of their linear correlation with the H-bonding energy, we have shortlisted five parameters (Electron density at the BCP: ρ, its Laplacian: $\nabla^2\rho$, Stabilization energy due to $n\rightarrow\sigma^*$ type charge transfer: E(2), Donor-Hydrogen distance and Hydrogen-Acceptor distance) to model linear equations for predicting E_{HB} values. We have performed single variable and multivariable linear regression analysis over the natural base pairs and modeled sets of linear relationships between these five parameters and E_{HB}. We test the performance of our model over the set of modified base pairs and obtained promising results, at least for the moderately strong H-bonds.

Atomistic and Coarse Grained Parameterization of Poly (lactic-co-glycolic acid) based polymers and their interactions with Lipid bilayer membranes

P26

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Poly lactic-*co*-glycolic acid (PLGA) and its variants (depending on the ratio of lactic acid and glycolic acid) have been among the most attractive polymeric candidates used to fabricate devices for drug delivery application [1]. However, the detailed studies of these drug delivery vectors at atomistic level needs to be deciphered in order to study their interactions with biological systems like lipid bilayers of the cells.

Molecular dynamics is one such prominent technique by which we can study these polymers at atomistic level. The present work focuses on the atomistic parameterization of PLGA based polymer systems using OPLS-AA force field. 11 different systems were taken depending on the ratio of lactic acid and glycolic acid to demonstrate the different PLGA based polymers. Of these 11 systems 10 mer chains, 50mer chains, 100mer chains, 5 chains of 10 mers and 125 chains of 10 mers were modeled to assess the validity of the defined parameters at different levels. Molecular dynamics simulations were carried out using Gromacs 5.1.2 molecular dynamics suite in three different solvent systems viz. aqueous, acetone and chloroform of all the modeled systems. Different parameters chosen to validate the parameters were solvent accessible surface area (SASA), radius of gyration in different solvent systems and solvent free energy and were correlated with the experimental values provided in the literature. Further analysis focused on the martini [2] parameterization of PLGA based polymers for their coarse grained (CG) molecular dynamics (4 to 1 mapping was chosen) simulations. Coarse grained molecular dynamics were carried out to reduce the computational efficiency achieved in atomistic simulations and to study the effect of these polymeric systems with biological systems like lipid bilayer (DPPC model).

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Combined Quantum Mechanics/Molecular Mechanics and Molecular Dynamics Study of Selective Nitration and Azidation of Aliphatic Carbon by the Halogenase SyrB2

P27

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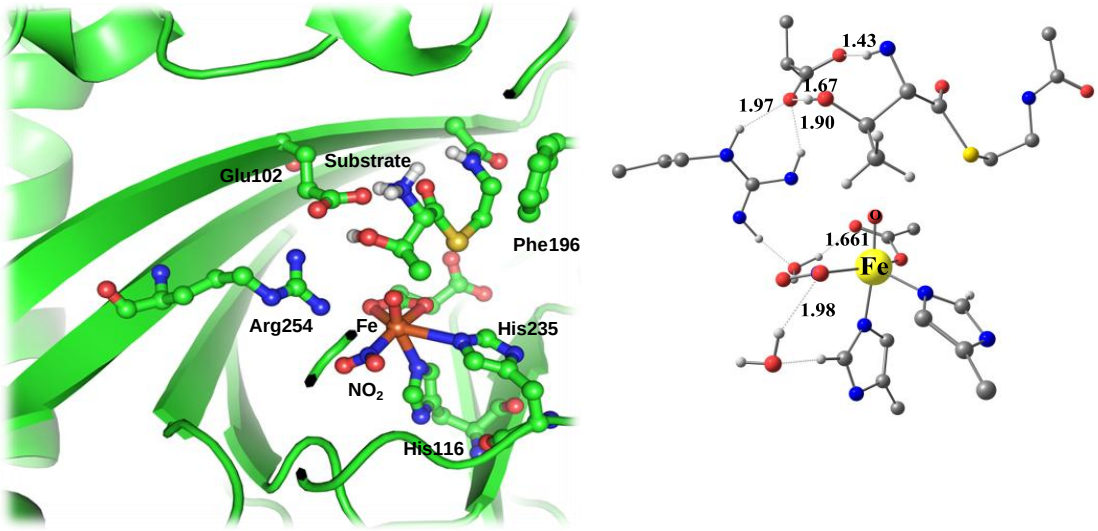
The enzyme SyrB2 catalyze the selective halogenation of L-threonine employing a Fe^{IV}-oxo species as intermediate. Combined quantum mechanical/molecular mechanical (QM/MM) calculations and molecular dynamics (MD) simulations has done to explore the complete mechanistic pathway of the selective halogenation process [1]. Further study showed that wild type halogenate SyrB2 can catalyze aliphatic nitration and azidation reaction in the same mechanistic way as the halogenation [2]. In the present work, we replace the chloride ligand by nitro in the active site of the SyrB2 protein and studied the complete mechanistic pathway of the nitration of the aliphatic carbon atom. Herein, we use combined quantum mechanical/molecular mechanical calculations and MD simulations to decipher the selective nitration process over hydroxylation.



a. 2ns MD snapshot of the SyrB2 (Chloride replaced by nitro) b. active site model for the oxoferryl species-substrate complex used in the DFT investigations on the reaction mechanism.

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Insilico Profiling of Deleterious Non-Synonymous SNP's in *ADRA-2* & *ADRB-2*

P28

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Mortality due to coronary artery diseases in India and elsewhere is now at alarming state. The disease claims itself to be the topmost cause of death among the non-communicable disease globally. The disease is caused due to varied reasons involving unhealthy lifestyle practices and certain non-modifiable risk factors. It is been believed that the disorder progress from second decade of individual's life. Any interventional adopted at early stage of life may delay the onset of disease. CVD being a hereditary disorder, diagnosing the substantial variations of genes responsible for this disease can help the individual to take interventional measures on time. Particularly, single nucleotide polymorphisms (SNPs) of alpha-2 adrenergic receptor (ADRA-2) and beta-2 adrenergic receptor (ADRB-2) play a vital role in the maintenance of systemic sympathetic activity and hence essential in the regulation of the cardiovascular responses such as blood rate and blood pressure. SNP variation in these genes causes faulty protein production and thereby results in thrombogenisis. The current study aims to identify such deleterious SNPs through *insilico* approach and to use them as a marker for diagnosing CVD. In-case of *ADRA2* from a total of **184** SNPs, **38** were found to potentially deleterious and V37G of which was determined to be highly deleterious. Similarly, for *ADRB2* from **162** SNPs, **36** were identified as potentially deleterious ones. I233T and T274M of *ADRB2* were resolute to be highly deleterious.

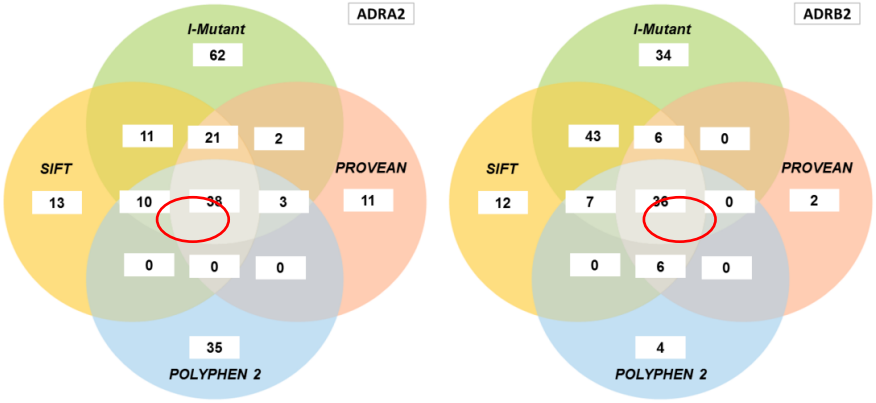

Figure 1: Venn diagram of *ADRA2* and *ADRB2* Deleterious SNP Prediction

Keywords: Coronary Artery Diseases, Receptor Gene, Thrombogenesis & Vasodilation

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Adsorption of neutral organic molecules on graphene and fluorographene based surface

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The adsorption properties of organic molecules on graphene and other 2D materials (such as fluorographene, graphene oxide, transitional metal dichalcogenides, hexagonal boron nitride, and phosphorene) have been found to be of potential in nanotechnology applications. The adsorption can be utilized for regulation of the electrochemical properties of materials [1]. A number of methods have been developed to covalently and non-covalently functionalize grapheme [2]. We employ first-principles calculations to study the effect of two-dimensional surface on the electronic structures of various small nonpolar organic molecules (acetone, acetonitrile, dichloromethane, ethanol, ethylacetate) as well as some electron deficient adsorbates. We have taken limited size cluster model to obtain reliable estimation of interaction energies. The accuracy of the calculated adsorption energies with various DFT methods are tested with benchmarking against CCSD(T) and MP2.5 results. The charge transfer and delocalization are mainly as a result of the π-conjugation and determines the strength and nature of noncovalent binding to surfaces.

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A Study on Non Linear Optical Properties of Newly Synthesised Triazino Quinolines

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Non linear optical materials play a pivotal role in the evolution of nonlinear optics and its impact in technology and industrial applications are excellent. **Non linear optical** properties of novel 4',7'-dimethyl-3-thioxo-1,2,4-triazinoquinolin-5-one and its six derivatives were studied. The molecular parameter was predicted by the theoretical investigation on the titled compounds using B3LYP functional with 6-31G (d, p) basic set and also carried out experimentally. The Determination of the energy gap, the dipole moment, the polarisability and the first hyperpolarisability explain that the molecules are the materials which can be used as effective NLO materials. The results are to be discussed in detail.

Insights into the Catalytic Mechanism of Porphobilinogen Deaminase

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Porphobilinogen deaminase (PBGD) catalyzes the formation of 1-hydroxymethylbilane (HMB) by a stepwise polymerization of four molecules of porphobilinogen (PBG). Structural and biochemical studies on PBGD have suggested residues with catalytic importance, but their specific role in the mechanism of the protein during catalysis is unclear [1]. Based on molecular dynamics simulations, arginine residues in the active site were hypothesized to play an important role in the deamination of substrate PBG [2]. To further understand the catalytic mechanism, quantum mechanical (QM) calculations were performed on a model system (R26, D99, dipyrromethane (DPM) cofactor and PBG) of human PBGD. The energies were calculated at M06/6-311++g(d,p) level of theory. The catalytic mechanism consists of 4 steps: (1) protonation of the substrate, PBG; (2) deamination of PBG; (3) nucleophilic attack on the deaminated substrate by the α-carbon atom of the terminal pyrrole ring of the enzyme-bound cofactor and (4) deprotonation at the same carbon position. Based on extensive QM calculations on the model system, it was observed that residue R26 donates a proton to the PBG moiety (Fig. 1). During the nucleophilic attack, the product formed is stabilized by the carboxylate side chain of the D99 residue. In the final deprotonation step, an extra proton from the penultimate ring of polypyrrole is transferred to R26 via D99, thus completing one cycle of catalytic mechanism. The deamination step was found to be rate limiting with an energy barrier of 46.63 kcal/mol.

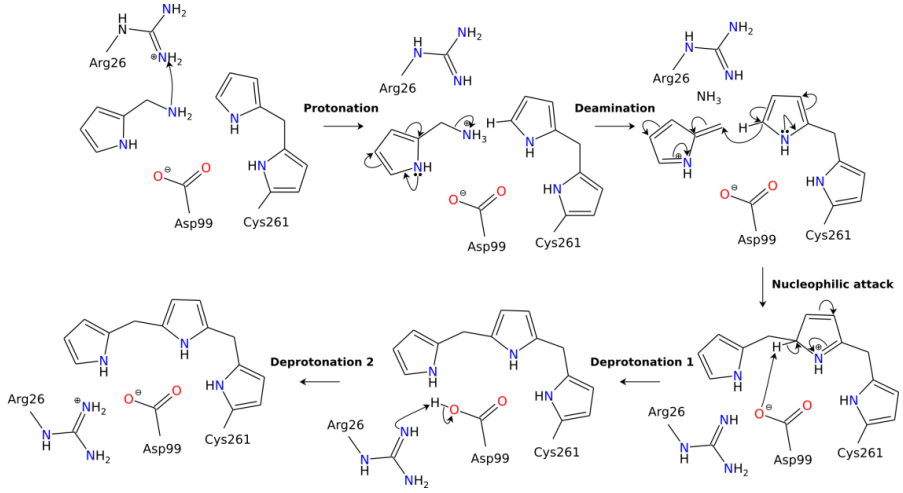

Figure 1: Schematic representation of human PBGD catalytic mechanism.

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Drug repurposing for ischemic stroke through integrated microarray analysis

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Classical drug development strategies against a disease are time-consuming and costly. Drug repurposing aims at identifying an already known compound to a new disease. This strategy overcomes the initial bottleneck in the drug development process, thereby saving substantial amount of time and money. This study aimed at repurposing FDA approved using network biology approach to treat ischemic stroke. Ischemic stroke is a common neurological disorder causing disability worldwide. In spite of the advances, the biology of the disease remains indefinite. miRNA and mRNA expression profiles in whole blood samples of ischemic stroke patients were downloaded from Gene Expression Omnibus. On analysis, 14 significant miRNA's and 27 significant mRNA's were obtained. Information on the FDA approved drugs and its targets were downloaded from drug bank. Pathway analysis was performed on the drug targets and the significantly altered genes. With the pathway analysis data, drug-gene interaction network was established using Cytoscape. Drug targets were prioritized by identifying the closely related pathways. The strategical analysis of the omics data has suggested new anti-ischemic compounds and gene targets that could possibly be used as biomarkers also.

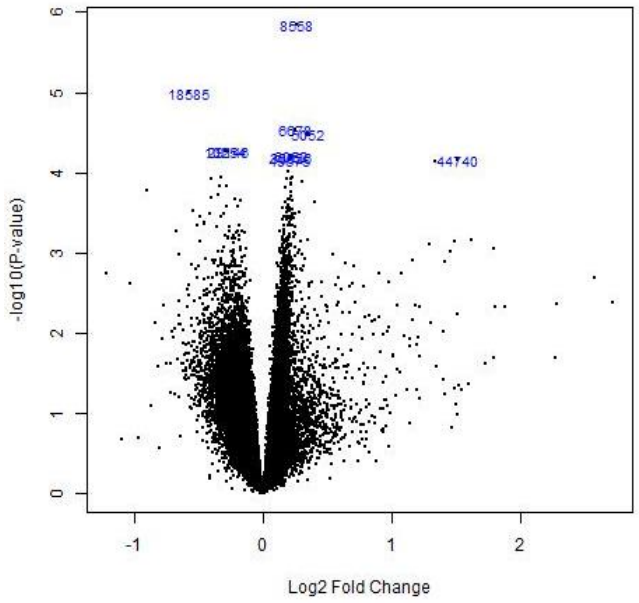

Fig1: Vocano-plot of the mRNA dataset

Structural dynamics of Kaempherol binding to the inflammation responsive protein ASC: a molecular dynamics study

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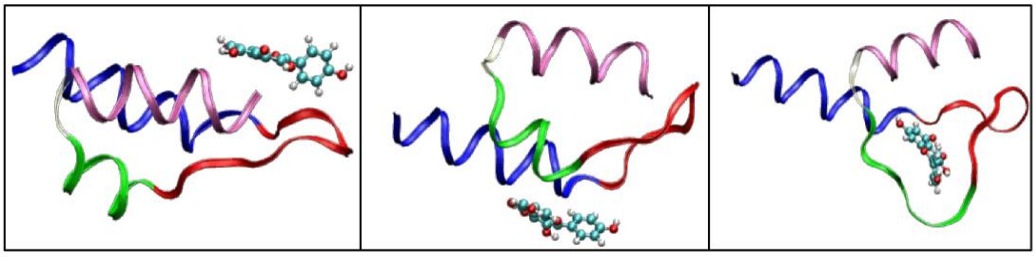
Kaempherol binding to the inflammation adaptor protein, ASC, is relevant for anti-inflammation associated with immune responses by altering the function of ASC via changes in its structure. ASC with six helices and 5 linkers is docked with kaempherol to find the binding sites and the structural dynamics of ASC-kaempherol complex is investigated using an all atom molecular dynamics simulation. Root mean square fluctuations of ASC backbone residues show significantly high fluctuations at the linker 2 and helix 3 in addition to the flucuations at the two ends when compared with the docked configuration. Root mean square deviations of the ASC backbones of the helix 3 and the linker 2 increases with respect to the initial ASC-kaempherol configuration after a certain period of time. The secondary structure analyses show conformational changes in the linker 2 and the helix 3 when bound to kaempherol after the same duration of time when the deviation started increasing. The minimum distance calculations between individual helices or linkers and kaempherol show that the linker 2 and the helix 2, 3 and 4 come closer to the kampherol after the same duration of time and then stay closest for the rest of the time. The covariance analysis demonstrates that ASC residues are highly correlated in presence of kaempherol. The linker 2 and helix 3 are negatively correlated with the two terminals and the linker 3, the helix 4 and the linker 4 indicating a motion opposite to each other. All the analyses direct towards a binding path of kaempherol where the kaempherol is initially located in an open pocket created by the linker 2, the helix 3 and 4. With time, the helix 3 moves in an opposite direction to the linker 3, the helix 4 and the linker 4 and is unfolded to wrap kaempherol up and attend a closed state to bind kaempherol driven by lowering in binding free energy. It has been found that the number of hydrogen bonds between ASC and kaempherol increases once the helicity of the helix 3 is lost and kaempherol binds to the closed pocket of ASC. The binding free energy of the ASC-kaempherol complex is found to be -44 kJ/mol using Bennett's acceptance ratio method. Our calculations reveals the mechanism of kaempferol binding to ASC via a conformational change in ASC which might alter the function of ASC as an inflammosome. This can be useful in building up a targeted therapeutic medication for inflammation in the future.



ASC-Kaempherol complex at different time steps

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Dihydrogen bonding in heterocyclic aromatic compound with alkali metal hydride - A theoretical study

P34

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Hydrogen storage plays an important role in many applications such as batteries, fuel cells, electric vehicles etc. In this work, we have studied the intermolecular dihydrogen bonding in heterocyclic aromatic compounds (C_4H_4O, C_4H_4S, C_4H_5N and C_5H_5N) with alkaline metal hydrides (LiH, NaH and KH). The constructed structures are optimized at B3LYP/6-311++G** and MP2/6-311++G** level of theory and found to be local minima from frequency analysis. To understand the molecular level properties we have taken geometrical, energetic and topological parameters derived from the Bader's theory. To analyze the existences of dihydrogen bond in considered structures we have performed Natural Bond Orbital analysis (NBO), Atom in Molecule (AIM) analysis, intermolecular energies and molecular electrostatic potential. The best suitable aromatic structure that forms dihydrogen bonding with the alkali metal hydride is identified.

Bioinformatics Identification of Drug Resistance Associated Genepair in Mycobacterium Tuberculosis A Review

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Tuberculosis is a chronic infectious disease caused by mycobacterium tuberculosis. Due to the extension use of anti-tuberculosis drugs and the development of mutations, the emergence and spread of multidrug resistance tuberculosis is recognized as one of the most dangerous threat to global tuberculosis control. In previous research they did not take into account and the emergence of transmissible drug resistance is connected with multiple gene mutations. In this study we use a bio informatics software GBOOST to calculate and interaction of single nucleotide pair and identify gene pair associated with drug resistance. This study provides deeper insights into the mechanism underlying anti-tuberculosis drug resistance, and the present method is useful for exploring the drug resistance mechanism for other organism.

KEY WORDS: Mycobacterium tuberculosis, drug resistance, gene pair and GBOOST.

Evaluation of Vitamin D, An Alternative on Interleukin-13 in the Treatment of Asthma - In Silico Approach

P36

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Asthma affects a majority of the world population. One among every 250 deaths is attributed to the current scenario worldwide. Asthma is a reversible airway process which is characterized by the airway hyper-reactivity, airway remodeling and inflammation. In relation to this disease, Interleukin-13 (IL-13) is one of the effector protein which plays a major role in signaling of mucin secretion, chitinase up-regulation, hyper reactivity in the airways and fibrosis. Mometasone, a chemically synthesized is the most commonly used medication for asthma patients to get a temporary relief from the bronchial constriction of the patient. By our present in Silico study, we hypotheisze that Vitamin D is an alternative supplement for mometasone as an efficient way to replace the side effects of mometasone which is commonly seen in the patients under treatment and we prove that interleukin-13 promises for its efficient therapeutic regulator in the molecular mechanisms of asthma via molecular docking and simulatory studies.

Identification of Proton Transfer Pathways in Different Variants of Human Carbonic Anhydrase II

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The rate determining step for the function of the enzyme human carbonic anhydrase II (HCA II) is known to involve an intramolecular proton transfer from the zinc bound water molecule to a histidine residue (His-64) located 8-10 Å away across the active site cavity [1]. The efficiency of this proton transfer step in the wild type enzyme is known to depend on the active site hydration as well as the orientation of His-64 sidechain [2]. In this work, we have investigated how the catalytically important proton transfer path at the active site of the enzyme is affected in the presence of its substrate,$CO_2$and some of its well-known inhibitors. Starting with a known high resolution crystallographic structure of the enzyme (with a substrate/inhibitor), a proton transfer pathway is defined as a hydrogen-bonded network formed by polar sidechain atoms of amino acid residues and water molecules at and around the active site that connects the origin and target atoms between which the proton needs to be transferred [2,3]. It is found that when the substrate CO_2 binds to the active site, no proton transfer path is evident from the crystal structure [4]. Upon binding at or near the active site by the inhibitors acetazolamide (AZM) [5] or 2-[(S)-benzylsulfonyl]-benzoic acid (3G1) [6], the key proton transfer path cannot be detected in the respective crystal structure. The inhibitor 6-hydroxy-chromene-2-thione (FC5) [7], known to inhibit the enzyme by occluding the entrance to the active site, surprisingly does not perturb the proton transfer pathway.

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Allosteric effect, role of cations and ligand binding mechanism in the *E. coli* TPP riboswitch

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The thiamine pyrophosphate (TPP) riboswitch regulates the levels of thiamine and its phosphorylated derivatives in the cell in response to the binding of TPP and Mg^{2+} ions [1,2]. The abundance of the riboswitch in bacteria and its absence from mammals makes it an ideal drug target. Although the crystal structure of the ligand-bound form (or "OFF" state) of the riboswitch has been reported, not much is known about the ligand-unbound form ("ON" state) [3]. Questions that remain to be addressed include details of structural changes occurring during the ON ⇌ OFF transition of the riboswitch, the role of Mg^{2+} ions, and the mechanism of ligand binding. The current study employs extensive molecular dynamics (MD) simulations to address these questions at an atomic level. Both TPP and Mg^{2+} are shown to be essential for bringing about the ON → OFF transition. A mechanism is proposed for the transmission of an allosteric effect from the ligand-binding site to the ribosome-binding site of the riboswitch. TPP binding follows a two-step mechanism: magnesium-mediated recognition of the pyrophosphate moiety followed by stacking of the pyrimidine moiety with bases in the binding site. Finally, the solvation dynamics of the Mg^{2+} ions during the binding process is elucidated. The findings complement experimental studies by providing atomistic detailed insights into the mechanism of functioning of the TPP riboswitch.

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Computational investigation of curcumin, a natural polyphenol that inhibits the destabilization and the aggregation of human SOD1 mutant (Ala4Val)

P39

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Aberrant aggregation in proteins leads to increased β-sheet propensity, thereby increasing the toxicity level. Numerous neurological disorders are triggered due to aggregation in protein. Superoxide dismutase 1 (SOD1) is one such protein that leads to Familial Amyotrophic lateral sclerosis, a devastating neurodegenerative disorder. In our study, the aggregation effect in native and the fatal mutant (Ala4Val) SOD1 was examined, using tConcoord. Experimental studies reported that the naturally obtained polyphenol have an inhibitory effect on the aggregated protein. Thus, we focused predominantly on curcumin, a natural occurring polyphenol to inhibit the aggregation in SOD1. In view of that, curcumin was computationally docked with both the native and mutant SOD1, using Autodock. Thus, our analysis suggested that curcumin showed the enhanced binding affinity in mutant SOD1 with increased hydrophobic interactions as compared to native SOD1. Further investigations were accomplished, using steered molecular dynamics and conformational sampling on both the bound complex of native and mutant SOD1 with curcumin, to unravel the effect of disaggregation. In addition, we also elucidated the variations in free energy landscape of native and mutant SOD1 in their unbound and bound states to differentiate the aggregation. Hence, the study postulated a classical treatment against mutant SOD1, using the naturally occurring polyphenol (curcumin) via the computational framework for designing the therapeutics against ALS [1].

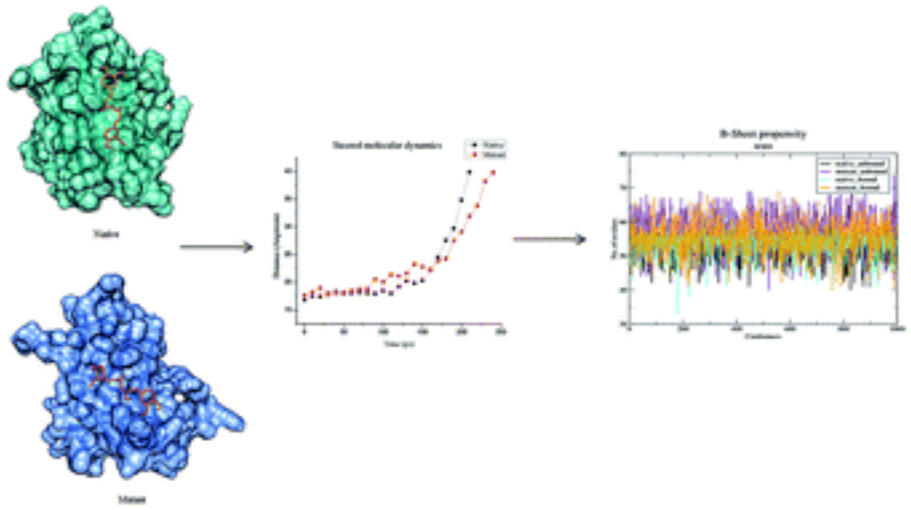

Figure representing the effect of curcumin on the native and mutant SOD1 proteins

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Study to Evaluate the Performance of High-Throughput Sequencing for Virus Detection –A Review

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High-Throughput sequencing method is a fast and cheap ways to sequence and analyse large genomes. The capacity of High-Throughput sequencing (HTS) for detection of known and unknown viruses makes it a powerful tool for broad microbial investigations, such as evaluation of novel cell substrates that may be used for the development of new biological products .This study evaluates the performance of High –Throughput sequencing for potential detection of viral adventitious agents by spiking model viruses in different cellular matrices to mimic putative materials for manufacturing of biologics. Four model viruses were selected based upon different physical and biochemical properties and commercial availability, human respiratory syncytial virus (RSV),epistein Barr virus(EBV),feline leukemia virus (FeLV) and human reovirus (REO). Data were obtained using different sequencing platforms and bioinformatics analyses were performed. This study highlights the potential for using HTS for sensitive detection of adventitious viruses in complex biological samples containing cellular background .

Keywords High Throughput sequencing, Adventitious viruses, Bioinformatics, Biochemical Properties

Molecular docking studies on 4-hydroxy-2*H*-thieno[3,2-*c*]quinolin-3-one with *thymus* DNA

P41

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The newly synthesised 4-hydroxy-2*H*-thieno[3,2-*c*]quinolin-3-one was subjected to the docking studies using c DOCK. After obtaining the results for ADMET property of the optimized titled compound, the ligand was docked with thymus DNA. The calculations and the results obtained were compared with the in-vitro results. The results are to be discussed in detail.

Exploration of Natural Compounds as Potential Inhibitors of TRAF6-Basigin Interaction in Melanoma Using Structure-Based Virtual Screening and Molecular Dynamic Simulations

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Melanoma is one of the least common but most fatal forms of skin cancer affecting around 132,000 people globally each year. With the constant depletion of earth's protective ozone layer more and more ultraviolet (UV) rays are reaching the earth's surface which has resulted in the global increase in melanoma cases. The interaction of the proteins tumor necrosis factor receptor-associated factor 6 (TRAF6) and Basigin (CD147) is known to be associated with the over-expression of matrix metalloproteinases (MMPs) in melanoma cells. MMPs are known to be responsible for melanoma metastasis. Hence TRAF6-BSG complex can act as a potential therapeutic target. In previous studies, amino acid residues Lys340, Lys 384, Glu417 and Glu511 of TRAF6 were identified as most vital residues on the basis of their contribution to interaction energy, relative solvent accessibility and electrostatic interactions in the TRAF6-BSG protein-protein interaction (PPI) interface. In our current work, we have performed structure based virtual screening of natural compounds obtained from ZINC database and some previous reports (n=16789) against TRAF6-BSG complex defining Lys340, Lys384 ,Glu417 and Glu511 as active site residues in GOLD 5.2 software. The molecules were first evaluated for drug-likeliness on the basis of Lipinski's parameter and ADMET properties (n=15000). After docking the molecules were analysed on the basis of their Gold Score fitness, Chem Score fitness and Chem Score DG scores. Finally, two potential inhibitors (ZINC 49048033 and ZINC 2095558) were identified which were observed to make electrostatic interactions with Lys384 of TRAF6 in the complex interaction interface. These ligands bound complexes were further subjected to molecular dynamic simulations and analysed for their molecular interactions. Results suggested substantial pharmacological importance of the lead molecules. From our studies we conclude that ZINC 49048033 and ZINC 2095558 can have great potential to act as inhibitors in melanoma metastasis.

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Novel splice variation based approach towards mining putative riboSNitches in MAPT pre-mRNA

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P43

RiboSNitches are single nucleotide polymorphisms (SNPs) which cause significant structural disruption in the pre-mRNA secondary structure ensemble leading to disease phenotype (Halvorsen *et al*, 2010). Till date they have been identified in the 5' and 3' untranslated regions of genes associated with the pathogenic conditions.

It has been reported (Warf *et al*, 2010) that in different types of alternative splicing events, variants are seldom related to pre-mRNA secondary structure. We worked on the hypothesis that the SNPs which lead to structural changes in pre-mRNAs may result in differential expression of splice variants. Our study focuses on lethal mutations and SNPs related to alternative splicing and structural methods based on riboSNitch mining tools. Accordingly, we examined the alternative splicing mechanism of exon 10 in MAPT/ tau gene, which is crucial for maintaining the natural balance between three and four repeat protein isoforms. It has been reported earlier (Ghetti *et al*, 2015) that disruption of this natural balance may result in differential expression of the MAPT isoforms, which in turn may lead to neurodegeneration. By pursuing this method it is possible to detect putative riboSNitches which may have been missed in the database of pathogenic SNPs identified by empirical correlation studies such as GWAS. Here we report three putative riboSNitches, which were not found in available pathogenic SNP databases. It is possible that these riboSNitches may be responsible for pathogenicity, in conjunction with other regulating factors.

This method of analyzing SNPs which affects the alternative splicing on the basis of structural changes, without the *a priori* knowledge regarding their pathogenicity, opens up a new approach towards riboSNitch prediction. Our analysis prepares the ground for designing further investigations for the experimental validation under *in vivo* conditions.

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Molecular recognition of ligands in multiple binding sites of Tetrahydrofolate riboswitch

P44

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In *Clostridiaceae* and *Lactobacillaceae* bacterial families, Tetrahydrofolate (THF) riboswitch acts as sensor for the biologically active reduced folate derivatives, including N5- and N10-modified THF. It regulates the genes associated with folate-related biosynthesis and transport by either terminating transcription or inhibiting translation upon ligand binding [1]. Two ligand binding pockets are observed in the THF riboswitch aptamer domain i.e. three-way junctional (3WJ) and Pseudoknot (PK) binding site. However, a subsequent study has revealed that although strong cooperative interactions occur between the ligands present at the 3WJ and PK-site, only the PK-site regulates gene expression upon ligand binding, whereas the other site plays a role in stabilizing the overall structure [2]. However, experimental studies described above do not reveal the extent to which each interacting aptamer nucleotide contributes to the overall binding strength of the ligand.

To fill this void, in the present study, we use a combination of quantum mechanical calculations and molecular dynamics simulations to analyze the molecular basis of ligand recognition at two different ligand binding pockets within the aptamer domain of the THF riboswitch. Our analysis reveals that the hydrogen bonding interactions between ligand and aptamer are more stable and rigid at the PK-site, compared to the 3WJ ligand complex (Figure 1). Overall, our studies may help in formulating a systematic approach to structural based drug design within these class of RNA, which may, in turn help in the development of RNA based therapeutics.

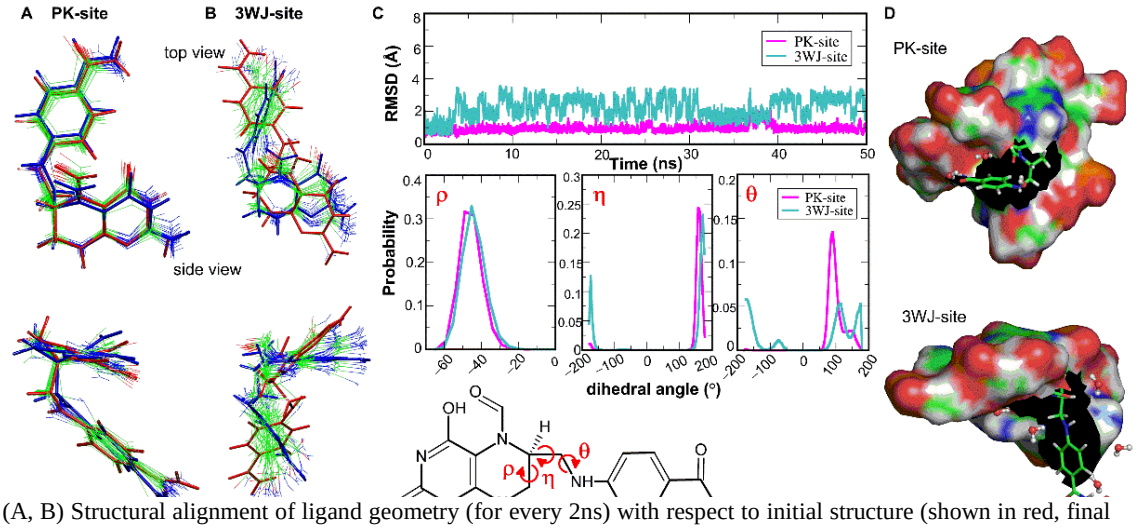

Figure 1. (A, B) Structural alignment of ligand geometry (for every 2ns) with respect to initial structure (shown in red, final structure shown in blue) in the PK-site and 3WJ-site. (C) RMSD plot for trajectory for ligands in the PK and 3WJ-site over the time course of 50ns simulation and probability distribution of dihedral angle (ρ, η and θ), corresponding to different torsions of functional group of ligands in the PK and 3WJ-site. (D) Ligand bound with PK and 3WJ-sites and interacting with surrounding water molecules.

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Evidence of ionic liquid induced bias in the disulfide bond isoform equilibrium of conopeptides from a molecular dynamics study

P45

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Ionic Liquids (ILs) having numerous specialized features and structural variability have proven useful for biomolecular reactions. Here, we exploit ILs to control the disulfide bond isoform equilibrium observed in cysteine rich conopeptides. Conopeptides, the toxins found in marine cone snail venoms, attack ion channels and neuroreceptors and have huge therapeutic importance. When synthesized, these peptides yield several disulfide bond isoforms, structural elucidation and separation of which are challenging [1-2]. Recent experiments indicate that oxidative folding of such peptides in certain ILs produce high yield of correctly folded native isoform. Using molecular dynamics simulations we aim to understand the reason behind such a biological recognition. Our simulations reveal the general aspects of ionic solvation in biomolecules. Detailed investigation into populations of the different disulfide bond isoforms of conopeptide AuIB in different aqueous IL solutions by replica exchange molecular dynamics reveals distinct trends, which might be related to the Hofmeister effect of the cation and anion of the IL and specific interactions of the aqueous IL solutions with the peptide [3].

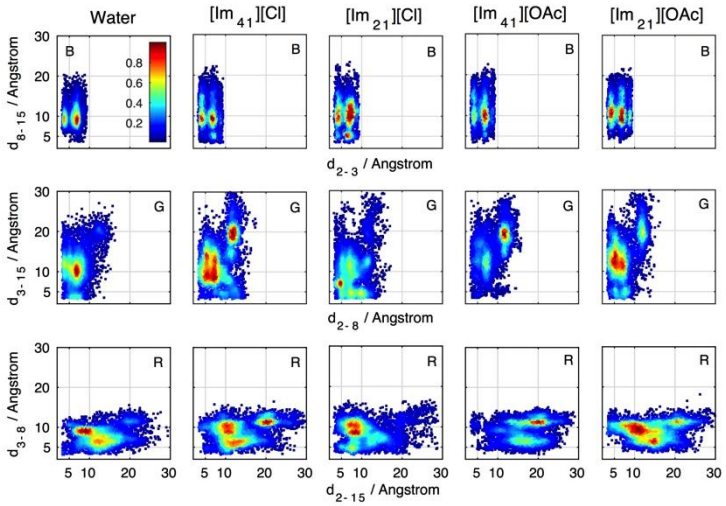

Fig. 1 S-S distance distributions for the three disulfide bond isoforms of AuIB (B: Beads, G: Globular and R: Ribbon) in neat water and four aqueous IL solutions. The plots show distribution of snapshots sampled in the lowest temperature replica alone and contain 5000 scattered points for the aqueous IL solutions and 4000 points for pure water.

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Hidden electrostatic basis of dynamic allostery in a PDZ domain

P46

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Allostery is a phenomenon in which ligand binding at a site is linked to the structural or dynamical changes at a distant site. Although, numerous models have been proposed to understand the molecular mechanism of allostery, a quantitative description of signal propagation still remains elusive. PDZ domains have been widely used as a model system to understand allosteric transition without structural changes where distal side chain dynamics is modulated upon ligand binding and the origin has been attributed to entropic effects.[1] In this work, we have speculated and explored the energetic basis of the observed "dynamic allostery" in a PDZ3 domain protein using molecular dynamics simulations. Our results suggest that ligand binding information propagates in the form of change in inter-residue interaction energies, especially towards the N-terminal residues and α1-β4 region. Interestingly, we find shift in the inter-residue contacts and accompanied side chain orientations as a reason for the large change in interaction energies at a distant region of proteins. Our analyses clearly demonstrate a "population shift" in the hydrogen bonded network and salt bridges upon ligand binding. Interestingly, the internal redistribution and re-wiring of side chain interactions lead to large cancellations resulting in a small change in the overall enthalpy of the protein, thus making it difficult to detect experimentally. This could be the reason for the prevailing focus on "dynamic" or "entropic" effects, whereas the energetics seems to be the more fundamental factor that drives allosteric effects in PDZ3 domain protein.[2]

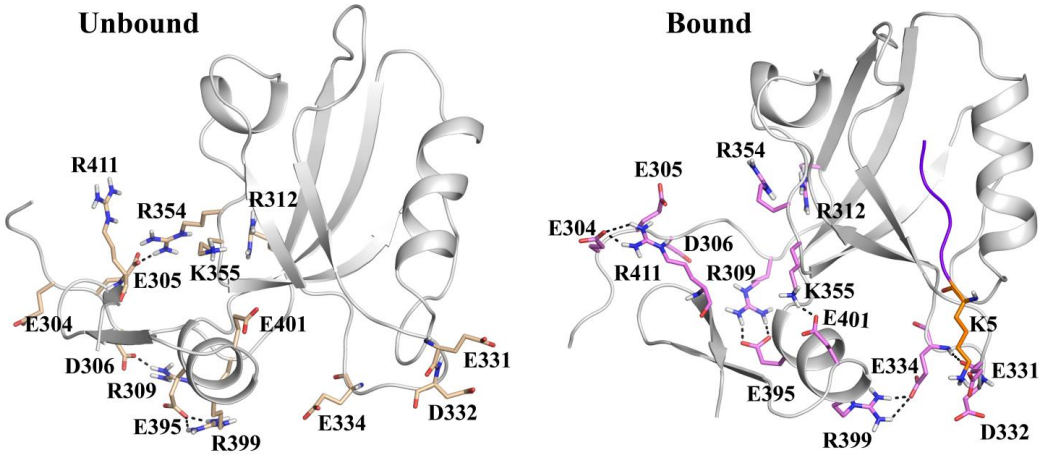

Figure: Rearrangement and rewiring of side-chain interaction network between unbound and bound states. Ligand binding information is communicated through change in sequential hydrogen bonding network.

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Going beyond base pairs: characterization of higher order structural elements in RNA

P47

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Characterization of RNA structural elements in terms of geometries and stabilities are important to understand the diversity in the structure, dynamics and functions of RNAs. A solid foundation was laid towards this goal in 2001 by Leontis and Westhof, who proposed a comprehensive edge specific classification and nomenclature scheme (LW scheme) for possible non-canonical base pairs [1]. In 2011, Almakarem *et al.*, have classified and annotated RNA base triples into 108 geometric families, simply by extending the LW approach [2]. However, this annotation scheme is not scalable to quartets and higher order structures, mainly due to lack of information regarding topology (arrangement of constituent nucleotide bases in terms of base pairing connectivities).

To overcome this limitation, here we propose a topology based characterization scheme for higher order structural elements in RNA. For this purpose, the RNA structure is represented as a graph (nodes represent nucleotides and edges represent base pairing connectivities). The connected components (of N nodes), therefore, represent the higher order structural elements in RNA (of N nucleotides). Such connected components present in the large RNA graph has been identified using Depth First Search algorithm. Again, different non-isomorphic forms of the connected graph element resemble the possible topological varieties of the corresponding RNA structural element. Here we also present (a) Quartet Finder, a tool to identify and annotate RNA quartets based on our proposed topology based nomenclature rules; (b) a database containing a topology wise listing of quartets present in reported RNA structures and (c) Quartets in RNA (QUARNA), a web server which integrates the tool and the database to provide a comprehensive platform for identifying, annotating and visualizing RNA base quartets. These collectively render diverse inputs towards hypothesis driven biological research.

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Characterization of cysteine thiol modifications based on protein microenvironments and local secondary structures

P48

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Protein microenvironments were reported earlier to be conserved around disulfide-bridged cystine motifs with similar functions, irrespective of diversity in protein sequences [1]. Here we report characterization of cysteine thiol modifications based on protein microenvironments, secondary structures and specific protein functions. Protein microenvironment around an amino acid was defined as the summation of hydrophobic contributions from the surrounding protein fragments and the solvent molecules present within its first contact shell [2]. Cysteine functions (modifications) were grouped into enzymatic and non-enzymatic classes. Modifications studied were—disulfideformation, thio-ether formation, metal-binding, nitrosylation, acylation, selenylation, glutathionylation, sulfenylation, and ribosylation. 1079 enzymatic proteins were reported from high-resolution crystal structures. Protein microenvironments around cysteine thiol, derived from above crystal structures, were clustered into 3 groups—buried-hydrophobic, intermediate and exposed-hydrophilic clusters. Characterization of cysteine functions were statistically meaningful for 4 modifications (disulfide formation, thioether formation, sulfenylation, and iron/zinc binding) those have sufficient amount of data in the current dataset. Results showed that protein microenvironment, secondary structure and protein functions were conserved for enzymatic cysteine functions, in contrast to the same function from non-enzymatic cysteines. Disulfide forming enzymatic cysteines were tightly packed within intermediate protein microenvironment cluster, have alpha-helical conformation and mostly belonged to CxxC motif of electron transport proteins. Disulfide forming non-enzymatic cysteines did not belong to conserved motif and have variable secondary structures. Similarly, enzymatic thioether forming cysteines have conserved microenvironment compared to non-enzymatic cystienes. Based on the compatibility between protein microenvironment and cysteine modifications, more efficient drug molecules could be designed against cysteine-related diseases.

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Effect of salt concentrations on stabilities of achiral and chiral (α-substituted) PNA-DNA complexes: A molecular dynamics study

P49

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Peptide nucleic acids (PNA) are synthetic oligonucleotides, which potentially mimic nucleic acids and have been proposed to be excellent candidates for a wide range of applications in antisense therapy and drug designing. Prior experimental studies have revealed enhanced thermodynamic stabilities of neutral PNA-DNA helices by incorporation of charged side chains on a neutral backbone. The structural and conformational properties of PNA-DNA, PNA-RNA helices have also been studied using molecular dynamics simulations. Despite these extensive studies, the effect of salt concentrations on charged and uncharged PNA-DNA helices at the molecular level has barely been explored. To investigate effects of salt (NaCl) concentrations on the stability of neutral and charged PNA at the atomistic level, molecular dynamics simulations have been carried out. We performed simulations of neutral (Gly substituted), positively charged (D-Lys substituted) and negatively charged (D-Asp substituted) PNA-DNA helices in four different salt concentrations (0, 150, 500, and 1000mM). Neutral and negatively charged PNA-DNA duplexes showed negative salt dependence, while binding affinity of positively charged PNA-DNA complexes increased with increasing salt concentration. Inter-strand Watson-Crick hydrogen bonding interactions were observed to be the driving force for stabilizing all the PNA-DNA helices. Hydration dynamics and counterion distribution analysis indicate electrostatic nature of interactions. Positively charged PNA-DNA was found to have higher binding affinities compared to negatively charged helices, while backbone conformation of DNA strand in PD duplexes is similar to B-form. The results of our MD simulations were able to capture the conformational behaviour of PNA-DNA duplexes and their nature in different salt concentrations. With this study, we conclude that chiral and physicochemical properties of substituents play an important role in stabilizing PNA-DNA duplexes, hence chirality if properly used can be exploited to improve the binding affinities of PNA strands towards DNA. Results obtained in these studies can be useful to make probes or better design of nucleic acid analogues.

Study of Ion Transport Across Carbon Nanotubes: A Molecular Dynamics Approach

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Study of ion transport through carbon nanotubes (CNTs) is interesting in its own right as carbon nanotube can act as synthetic ion channel which mimic the selective properties of biological ion channel. In order to trace the selective behavior of the Na^+ through various zig-zag carbon nanotubes of length 4.6 Å and dimensions (19,0), (17,0), (16,0), (15,0), (14,0), (13,0) embedded in POPC lipid bilayer immersed in 0.1 M NaCl, we have used all atoms molecular dynamics simulation using GROMACS 5.1.4 package. The equilibrium was performed initially at the NVT ensemble and latter at the NPT ensemble for total 1000 ps, this is followed by production run in the NPT ensemble for 100 ns with the time step of 2 fs. The total no of permeation events of water and ions are calculated. The structure obtained at the end of the above simulation was used as the initial structure for the umbrella sampling simulation. Windows are generated with respect to 0.05 nm intervals, simulations were performed for each window for 500ps . The weighted histogram analysis method (WHAM) was used to compute the potential of mean force (PMF) for the transport of ion along the reaction coordinate.

On comparing the potential mean force (PMF) for Na^+ transport for the different CNTs, we observed that free energy profiles of sodium ion under different radii have different energy barrier as the ions traverse across the CNTs. It is observed that the energy needed for ions to pass through CNTs of dimensions (19,0), (16,0), (15,0) and (13,0) with radius ranging from 7.08 Å to 5.00 Å are found to be -3.2, -5.0, -6.0, -8.0 kcal/mol respectively. In other words, wider CNTs are found to be more feasible for ion permeation than the narrow one. This can be explained as ions encounter an energy barrier mainly arising from dehydration, when they try to pass through the narrow CNTs, they need to peel off/strip of some solvent molecules before they get into CNTs, This observations are comparable to that of observed in a biological ion channel. The radial distribution function of water-oxygen and water-hydrogen atoms around the Naare calculated in different dimensions of CNTs considered. The coordination numbers of waters around the ions in the first hydration shell is also measured for different CNTs. Ion occupancy which describes as the numbers of ions present inside the CNTs in the fraction of time, also calculated from different CNTs. Our results provide in depth understanding of the mechanism of ion transport in the synthetic ion channel and provide information about how the selectivity and feasibility of ion diffusion are largely affected by the dimensions of CNTs.

Base-calling Implications of the "16" IUB-IUPAC codes Probability Conservation Equation

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Assuming that Base-calling during DNA-sequencing is **NOT** mutually, exclusive, we have the Probability of Union of "4" bases/ nt (A: Adenine | C: Cytosine | G: Guanine | T: Thymine) is as given by the Identity below:-

$P(A \cup C \cup G \cup T) = P(A) + P(C) + P(G) + P(T) - P(A \cap C) - P(A \cap G) - P(A \cap T) - P(C \cap G) - P(C \cap T) - P(G \cap T) + P(A \cap C \cap G) + P(A \cap C \cap T) + P(A \cap G \cap T) + P(C \cap G \cap T) - P(A \cap C \cap G \cap T)$

The equation above contains 4 "singlets", 6 "doublets", 4 "triplets" and; 1 "Quadruplet" (which being essentially an intersection of ALL 4 bases can be safely considered to be a "GAP" denoted by ' - ' as in sequence alignments).

Interestingly, sum-total of these terms (including LHS, union of ALL 4 bases being "N" = aNy base and excluding Gap) = 4 + 6 + 4 + 1 = 15.

And, the IUB-IUPAC codes are as well exactly "15" in number (cf. http://biocorp.ca/IUB.php)

Additionally, we can Back-substitute for the intersection terms in the above Master equation by for example considering the base-triplet **B** = Not A = { C, G, T }.

$P(C \cup G \cup T) = P(C) + P(G) + P(T) - P(C \cap G) - P(G \cap T) - P(T \cap C) + P(C \cap G \cap T) =$ **P(B)**

That is, we convert each "Intersection" term, alternately expressing them as "Union" terms, which is a logical approach given the IUB-IUPAC codes, for example, Y (pYrimidine) = (*C* ∪ *T*), *written in-short as CT.*

As we are still left with "Doublet Intersection" terms in the second equation for ***P(B)*** *above, we resort to, for instance:-*

$P(T \cup C) = P(T) + P(C) - P(T \cap C)$

which can be translated to,

$P(T \cap C) = P(T) + P(C) - P(T \cup C) = P(T) + P(C) - P(\mathrm{Y})$

In its entirety, a systematic Back-substitution of Union terms to replace ALL intersection terms as per the rationale explained above shall be dealt with and discussed in my Poster presentation, also drawing Due Attention to the **Base-Calling implications of this so-called "Probability Conservation" equation,** with additional key correlations based upon De Moivre's identities (for "Doublets" and "Triplets") and Chargaff's Parity rules (for "Singlets").

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http://dx.doi.org/10.7490/f1000research.1112352.1

High level quantum mechanical study on molecules containing planar tetracoordinate centers

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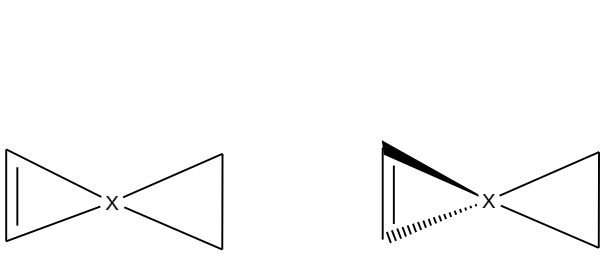
Over the past few years, the designing of new molecules and understanding their structure, stability and reactivity has been paid much attention. Here, we have undertaken a quantum mechanical study of the bicyclic ring complexes, **C_4H_4X** (X = C, Si, Ge, B^-, Al^-, Ga^-, N^+, P^+ and As^+), where X can form both planar and tetrahedral coordination (Figure). The planar tetra coordinate carbon is the preferred geometry over the conventional tetrahedral coordination in C_5H_4 molecule. Similarly, the isoelectronic B^- and N^+ also prefer the planar tetra coordinate environment. The isoelectronic third row elements Ge, Al^- and P^+ and the fourth row elements Ga^+ and As^+ except Ge prefers the tetrahedral geometry. The bonding in these complexes is explained using EDA-NOCV analysis. The stability of these molecules towards the ring opening reactions have also been studied.



X = C, Si, Ge, N^+, P^+, As^+, B^-, Al^- and Ga^-

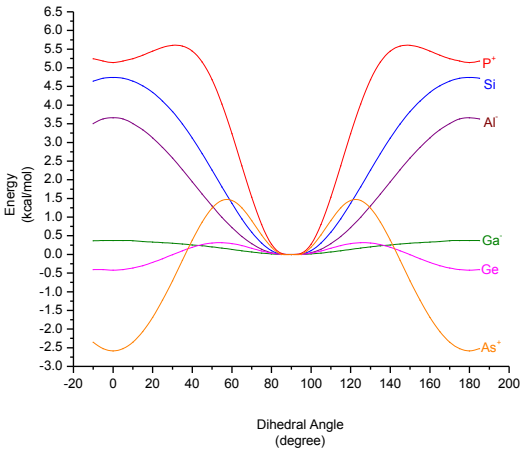


Figure: Variation of energy with respect to change in dihedral angle of ptX (X = Si, Ge, Al^-, Ga^-, P^+ and As^+)at the MP2/cc-pVTZ level of theory.