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Automated *de novo* Electron Density Map Tracing for the Structural Genomics Era

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Structural genomics initiatives around the world have gained momentum in recent years. An early step in such projects is the tracing of initial electron density maps, and this remains a challenging step requiring significant expertise. Map interpretation is especially demanding at lower resolutions, or when there are errors associated with the phase information. Two methods of tracing electron density maps have been implemented in the crystallographic modeling environment, QUANTA. The first method is optimal for high-resolution (≥ 2.0 Å) data sets, and involves simultaneous multiple-path analysis to identify the optimal path of the protein chain in skeletonized representations of electron density maps. In the second method, a secondary structure pattern analysis of skeletonized electron density maps is carried out, and then the secondary structure elements (alpha helices and beta strands) are converted to an all alpha-carbon representation, and extended to structural features such as turns and loops. The second method improves on the limitations of existing auto-tracing programs by extending the effective low-resolution limits from ~ 2.9 Å to ~ 4.0 Å.

Here we present results of the two tracing methods when applied to datasets with different resolution limits and figures of merit. The resultant alpha carbon traces, as well as all-atom models (built with QUANTA), are compared to the respective published structures. The two methods are extremely robust and fast (less than a second for the high-resolution tracing, and less than five minutes for the low-resolution tracing), and can trace the majority of alpha carbons in electron density maps with figures of merit as low as 0.5.

Keywords: de novo map tracing, X-ray crystallography software, automation in crystallography

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Elucidation of Structural Models of Formyl Peptide Receptors, FPR & FPR2, and Identification of Features, Responsible for their Differential Ligand-Binding Affinities

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Formyl peptide receptors are glycoproteins and belong to a broad category of G-Protein Coupled Receptors (GPCR) of Rhodopsin family. Invading pathogenic microorganisms and mitochondria on metabolism release fMLP and other formyl peptides. These peptides, upon binding to a neutrophil formyl peptide receptor (FPR), form a ligand-receptor-G-protein complex, which triggers several intracellular signals through G-coupled protein pathway and a series of biological actions such as chemotaxis, superoxide anion productions and enzyme secretion [1]. Although the inflammatory response inducing ligand, fMLP bind to FPR with high affinity, it interacts with a homologous chemotactic receptor, FPR2 with 400-fold less efficiency. Knowledge of structural details about formyl peptide receptors is crucial to understand the mechanism of chemoattractant receptors and design of anti-inflammatory drugs. In the present work, structural models of FPR and FPR2 have been developed with the application of homology modeling technique. An attempt has been made to identify structural features in FPR & FPR2, which are responsible for their significantly different ligand-binding affinities.

[1] Rathore R.S., *Biopolymers (Peptide Sci.)*, 2005, 1-14, *in press (early view)*.

Keywords: homology modelling of proteins, protein structure prediction, G-protein coupled receptor

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Structural and Docking Studies of β-lapachone Derivatives

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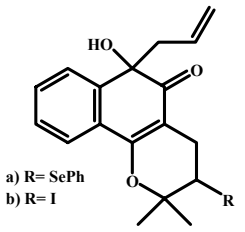
As it was shown that β-lapachone is active against *Trypanosoma cruzi* and that its 3-allyl derivative is not inactivated in blood, thus suppressing tripomastigote infectivity, compounds (a) and (b) were synthesized and studied. The pentahydro-5-oxaphenanthrene moieties of both structures are almost identical, rms deviation of the superposition of the 14 atoms being 0.052 Å. Molecules are packed in a same ladder fashion through OH...O, CH...O and CH...π (in (a)) interactions.



Docking studies were carried out with DOCK3.5 [1,2], for (a) and (b) and their dione analogs modelled based on the crystal structures, in the active site (AS) and the interface site (IS) of human gluthathione and *T. cruzi* trypanothione reductases (GR and TR). For the modelled dione ligands, it was possible to choose a preferred orientation in each site with total energies of *ca* -20 kcal/mol in TR-AS, -28 kcal/mol in TR-IS and GR-AS and -30 kcal/mol in GR-IS. On the other hand, docking studies with (a) and (b) did not show any preferred orientation. These results are in agreement with the showed trypanocidal activity, *in vitro,* of the dione derivatives and the inactivity of (a) and (b).

[1] Shoichet B.K., Kuntz I.D., *J. Mol. Biol.*, 1991, **221**, 327. [2] Shoichet B.K., Bodian D.L., Kuntz I.D., *J. Comp. Chem.*, 1992, **13**, 380.

Keywords: docking, drug-receptor modelling, stereochemistry

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Homology Modeling of *Xanthomonas citri* Molybdate-binding Protein

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We propose a molecular model for molybdate-binding protein (ModA) of the plant pathogen *Xanthomonas citri* based on homology modeling using *Escherichia coli* ortholog as a template. Alignments of ModA amino acid sequences were carried out using the BLASTp, Psi-BLAST and ClustalW. The rigid and dynamic molecular modeling of *Xac* ModA protein were obtained with Modeller and Gromacs, respectively. The results and the model were analysed with Sting Millenium. The built model contains two nearly symmetrical domains separated by a hinge region where the substrate-binding site lies. The first domain consists of 5 α-helix (52 amino acids) and 5 β-sheets (26 amino acids) and the second domain has two more β-strands than the first. The Ramachandran plot for the models shows 95,59% residues in the favorable regions and none is in the disallowed regions, as calculated with the program PROCHECK. Values of rmsd for *Xac* ModA X *E. coli* and *Xac* ModA X *A.vinelandii* were 1.5A and 1.9A, respectively. Comparisons between *X. Citri* ModA model and the structure of the *E. coli* and *Azotobacter vinelandii* orthologs have been done.

The ongoing biochemical characterization in combination with the structural analysis will assist the elucidation of the structure-activity relationship in regulating the uptake of molybdate in *Xanthomonas*.

Keywords: ModA, ABC transport system, molecular modeling