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Abstracts Book

Ilustração da Capa: Alexandre T. Bando

C.046 - Towards optimization of molecular recognition of neurotoxic aggregates by therapeutic agents

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INTRODUCTION Understanding molecular mechanisms of recognition and inhibition of neurotoxic aggregates by therapeutic agents (drugs and conformational antibodies), and optimization of their delivery to the central nervous system is important for development of efficient therapies against neurodegeneration. OBJECTIVES Initial selection and optimization of therapeutic agents targeting pathological misfolding and aggregation of proteins implicated in neurodegeneration with the new molecular modelling platform, accounting for structural restraints derived from the experiments on conformational antibody recognition of toxic oligomers. MATERIALS AND METHODS Solvation effects are among major factors defining pathways of proteins misfolding and aggregation, as well as compounds translocation through the blood brain barrier (BBB). Statistical-mechanical, 3D-RISM-KH integral equation molecular theory of solvation in a single formalism efficiently accounts for electrostatic and non-polar solvation effects, hydrophobicity, solvent mediated hydrogen bonding, and structural solvation. The theory is implemented in a number of software packages, including MOE and AmberTools (solvation structure and thermodynamics analysis), Amber molecular modelling package (multi-time-step MD steered with 3D-RISM-KH effective solvation forces). A new 3D-RISM-Dock scoring function with statistical-mechanical potentials of mean force for ligand and solvent degrees of freedom is coupled the with AutoDock program. DISCUSSION AND RESULTS We review recent developments in the 3D-RISM-KH theory and its applications for studying aggregation pathways of Amyloid β (Aβ) peptides, design and optimization of anti-prion therapeutic agents. New descriptors of hydrophobicity and aggregation propensity are introduced and used to build and screen structural models of Aβ oligomers . CONCLUSIONS The 3D-RISM-KH theory efficiently describes solvation effects (both thermodynamics and structure) with accuracy comparable to explicit solvent simulations. It provides a new insight into structural properties of neurotoxic oligomers and can be used for optimization of therapeutic agents. Supported by : This work is supported by the Alberta Prion Research Institute, Alberta, Canada. Keywords: Protein misfolding and aggregation, 3D-RISM-KH molecular theory of solvation, neurodegeneration

C.047 - Improving binding affinity prediction by using a rule-based model with physical-chemical and structural descriptors of the nano-environment for protein-ligand interactions

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INTRODUCTION Providing accurate predictions of protein-ligand binding affinities is extremely important for the success of computer-based drug discovery campaigns, especially the ones that rely on molecular docking programs to perform screening of small organic compounds. However, docking scoring functions are generally weak binding affinity predictors mostly because they fail to model properly polar aspects of the protein-ligand interaction, as well as the binding pocket geometric constraints. OBJECTIVES In order to improve binding affinity prediction, we developed a new scoring function, named STINGSF, derived from physical-chemical and structural features that describe the protein-ligand interaction nano-environment of experimentally determined structures. MATERIALS AND METHODS Relying mostly on descriptors from the BlueStar STING database (developed by the Embrapa's Computational Biology Research Group), STINGSF was built by training a ruled-based model with 1105 complexes from the PDBbind refined set using CUBIST, a nonparametric machine learning algorithm. DISCUSSION AND RESULTS Statistical analysis of the STINGSF's underlying model showed that descriptors that quantify the capacity of binding site residues to establish polar contacts with ligand's atoms are important in terms of predictive performance. For comparative evaluation with well-established protein-ligand scoring functions, we used the PDBbind benchmark v2007, the de facto standard for validation of scoring functions. Benchmark's results showed that STINGSF ranks among the best with regard to binding affinity correlation. CONCLUSIONS Keywords: protein-ligand interaction, scoring functions, machine learning

C.048 - HUMAN SUPEROXIDE DISMUTASE 3 – IN SILICO ANALYSIS

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INTRODUCTION Oxidative stress is involved in the development of several diseases, and extracellular superoxide dismutase (SOD3) is a major extracellular antioxidant enzyme. OBJECTIVES In this work, the effects of three variants of SOD3 on protein structure and function were evaluated using predictive computational methods, modeling and molecular dynamics. MATERIALS AND METHODS Ten algorithms were used for functional analysis of the following SOD3 variants: I-mutant, SNPs&Go, nsSNPAnalyzer, PhD-SNP, SIFT, Pmut, MutPred, SNAP, SNP Effect and PolyPhen. Four algorithms were used to generate theoretical models of the wild type (WT) SOD3 structure: Rosetta, Swiss Model, Modeller and I-Tasser. These models were aligned with the WT structure using the TM-align algorithm, and RMSD values were used along with results of the three secondary structure prediction algorithms: JPred, Jufo and PsiPred, to elect the best model. In silico mutagenesis was used to create mutants. Molecular Dynamics (MD) simulation was performed using the GROMACS software. DISCUSSION AND RESULTS According to the algorithms used to study the functional effect of SNPs, A58T was classified as neutral by 8 of them, and according to FoldX, it enhances the protein stability. A91T was classified as neutral by 7 algorithms, but according to FoldX, it decreases the protein stability. R231G was classified as neutral by 6 algorithms. The RMSD values from the alignment between the Protein Data Bank SOD3 structure and the generated models varied from 0.07 to 0.72, indicating that the generated models are reliable. The MD simulations generated four theoretical models (WT and mutants). The mutations resulted in structural changes when compared to the WT. CONCLUSIONS These results show that mutations in SOD3 affect both function and structure, indicating that it may be involved in the development of diseases related to oxidative stress. Supported by : FAPERJ, CAPES-DAAD, CNPq and UNIRIO. Keywords: computational predictions, oxidative stress, SOD3