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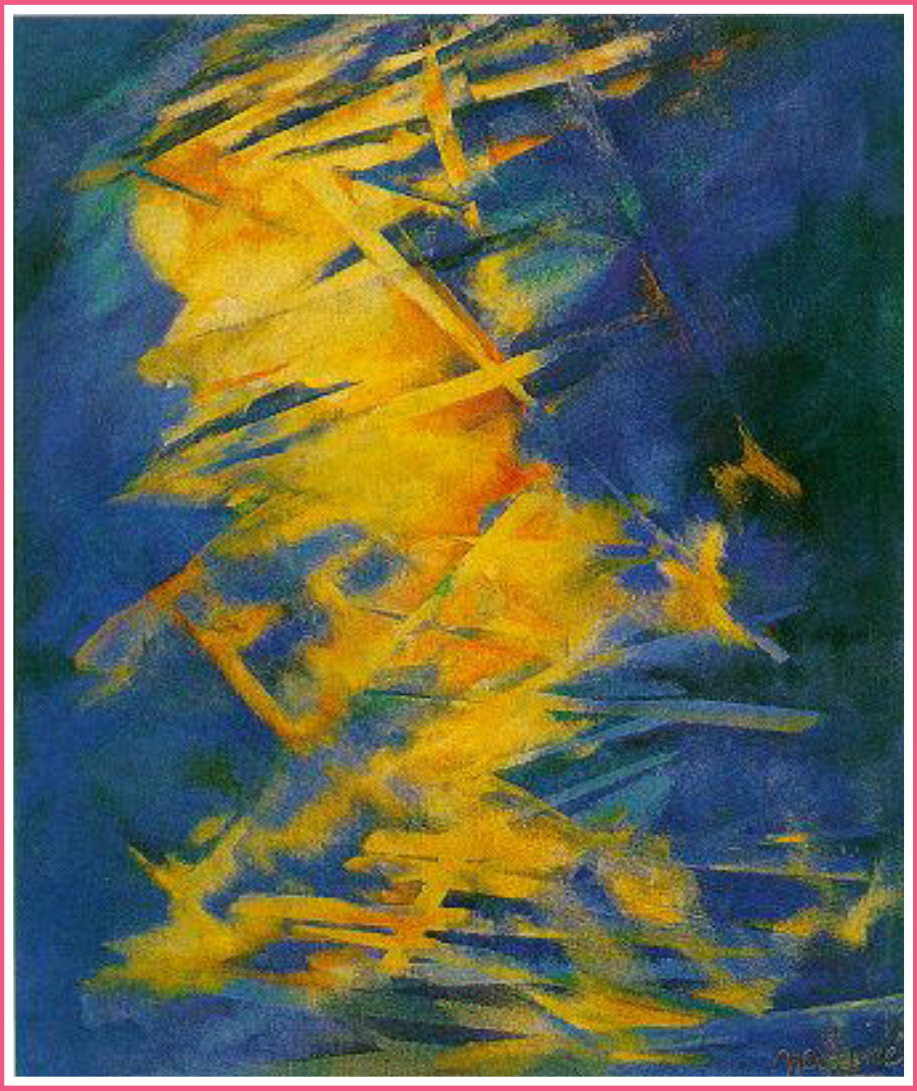

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XXIX ANNUAL MEETING OF ARGENTINE SOCIETY OF PROTOZOOLOGY (SAP)

November 13 -17, 2017
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Copasi

(603) **MULTIPLE TEMPLATE BASED HOMOLOGY MODEL OF ACTIVE STATE D2 DOPAMINE RECEPTOR**

Ignacio Exequiel Lobón (1, 2, 3), Maria Lucrecia Bogado (1, 2, 3), Emilio Luis Angelina (1, 2, 3), Adriano Martin Luchi (1, 2, 3), Gladys Laura Sosa (2), Nelida Maria Peruchena (1, 2, 3)

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Dopamine is an essential neurotransmitter in the central nervous system and exerts its effects through the activation of five subtypes of G protein coupled receptors (D1 to D5). Among subtypes, D2 has high therapeutic relevance for treatment of Parkinson's disease, schizophrenia and other disorders in the central nervous system. While D2 structure has not been solved yet, an homology model (HM) of D2 based on the known structure of the closely related D3 was reported. In the solved structure D3 has been captured in its inactive state, therefore the resulting models also would be in the inactive state.

In this work we constructed an HM of D2 in the activated, G protein coupled state. To build the model two templates were considered: D3 (PDB-ID: 3PBL) due to its high degree of sequence identity to D2 (78% in the TM helices) and the fully activated b_2 adrenergic receptor (PDB-ID: 3SN6) to model mostly the intracellular region of the receptor in the activated, G protein coupled state.

Sequence of D2 in its long form (NP_000786.1) and of Gi protein inhibitory alpha subunit (PDB-ID: 1GP2) were aligned with the template sequences. The alignment was then used to construct several 3-D models of D2 with the program Modeller 9.15. The model with the lowest value of the Modeller objective function was subjected to quality assessment with PROCHECK. The model was then inserted into an heterogeneous biological membrane using CHARMM-GUI server and subjected to MD simulations with Amber14 for further refinement, in order to get a 3-D modelcloser to the native form of the protein.

HM based on a single model requires the choice of a crystallized structure highly similar to the receptor under study, while the strategy used in this work, of alignment with multiple models, involves the excision of the receptor in several domains and the subsequent selection of the most appropriate template for each of these domains, this strategy being very useful to increase the accuracy of the models.

Keywords: Dopamine Receptor, Homology modeling, G Protein.

(1311) **MULTISCALE APPROACH TO THE ACTIVATION AND PHOSPHOTRANSFER MECHANISM OF CPXA HISTIDINE KINASE REVEALS A TIGHT COUPLING BETWEEN CONFORMATIONAL AND CHEMICAL STEPS**

Osvaldo Burastero (1, 2), Franco Marsico (1, 2), Lucas Alfredo Defelipe (1, 2), Elias Daniel López (1, 2), Mehrnoosh Arrar (3), Adrian Gustavo Turjanski (1, 2), Marcelo Adrián Marti (1, 2)

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Sensor histidine kinases (SHKs) are an integral component of the molecular machinery that permits bacteria to adapt to widely changing environmental conditions. CpxA, an extensively studied SHK, is a multidomain homodimeric protein with each subunit consisting of a periplasmic sensor domain, a transmembrane domain, a signal-transducing HAMP domain, a dimerization and histidine phospho-acceptor sub-domain (DHp) and a catalytic and ATP-binding subdomain (CA). The key activation event involves the rearrangement of the HAMP-DHp helical core and translation of the CA towards the acceptor histidine, which presumably results in a autokinase competent complex.

In the present work we integrate coarse-grain, all-atom, and hybrid QM-MM computer simulations to probe the large-scale conformational reorganization that takes place from the inactive to the autokinase competent state (conformational step), and evaluate its relation to the autokinase reaction itself (chemical step). Our results highlight a tight coupling between conformational and chemical steps, underscoring the advantage of the CA walking along the DHp core to favor a reactive tautomeric state of the phospho-acceptor histidine. The results represent not only an example of multiscale modelling, but also show how protein dynamics can promote catalysis.

Keywords: Coarse Grain; QM/MM; Histidine Kinase; CpxA; two component system.

(566) **STUDY OF THE MICRO RNA PRECURSOR PROCESSING MECHANISM BY QM/MM COMPUTATIONAL SIMULATIONS**

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Rnase III is the main protein in the processing of microRNA precursors (pri-miRNA) in bacteria. It is composed by two domains: dsRBD, which recognizes and binds the target precursors, and RIIID, which processes the pri-miRNA. The processing by RIIID is performed through a hydrolysis reaction, in which there is a nucleophilic attack on the phosphate group of the RNA backbone by an activated H_2O molecule or a OH^- ion previously coordinated to a Mg^{2+} ion of the active site. The proposed mechanism on this reaction is based on structural studies that are not able to capture the thermodynamics of the process, nor the protonation states of the residues and solvent molecules involved in the mechanism with atomistic detail. In this regard, computational simulation techniques can provide useful and detailed information about the reaction mechanism.

To study the hydrolysis mechanism through hybrid quantum mechanics/molecular mechanics (QM/MM) methods, we performed 50 ns of classical molecular dynamics (MD) simulation on the initial system. Next, we carried out 30 QM/MM steered molecular dynamics (SMD) simulations from different structures taken from the previous MD, in which we forced the nucleophile to attack the phosphate group. The irreversible work obtained in each SMD was used to calculate the free energy profile of the reaction, through the Jarzynksi equality.

Our results show that the the nucleophile is an OH^- ion and not a H_2O molecule, as the former's energy barrier is considerably lower. Additionally, the network of hydrogen bridges around the active site is important for its regeneration after the reaction. On the other hand, by mutating key residues on the active site which bind the Mg^{2+} ion, we observed that its role is not only activating the nucleophile, but arranging and stabilizing the active site by neutralizing the negative charge of the phosphate, nucleophile, and protein residues.

Keywords: microRNA, QM/MM, hydrolysis mechanism.

(1166) **TARGETING THE TRPV1 CHANNEL TO FIND NOVEL ANTIEPILEPTIC AGENTS. FROM MOLECULAR MODELING AND DOCKING SIMULATIONS.**

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Laboratorio de Investigación y Desarrollo de Bioactivos

Transient receptor potential cation channel subfamily V member 1 (TRPV1) is a nonselective cation channel modulated by both endogenous and exogenous ligands, pH, temperature and voltage. Many efforts have been made from industry and academia to find novel drugs that modulate the channel activity without undesirable side effects. Besides most of the research is focused on inhibiting the channel to get an antinociceptive effect, in the last few years it has been proposed as a promising target to treat some forms of epilepsy.

Since the 3D structure of the hTRPV1 is not currently available, we have constructed a homology model of the channel. The model was later refined in a membrane specific framework implemented