KA.09 - Modeling the Reactivity of Iron-Sulfur Proteins

Felipe Curtolo[1], Murilo Hoias Teixeira[1], **Guilherme Menegon Arantes [1]**
[1]Biochemistry, Instituto de Química da Universidade de São Paulo (Sao Paulo, Brazil)

Iron-sulfur (FeS) clusters are essential metal cofactors, comprising the largest class of metalloenzymes. They are involved in a wide variety of catalytic functions such as natural photosynthesis and cellular respiration. From structural and electronic points of view, FeS clusters sit between transition metal atoms and solids. Their electronic structures show many low-lying and near-degenerate states that may cross, leading to multiple-state reactivity. In polynuclear FeS clusters, strong electron correlation and long-range spin coupling effects complicate enormously the theoretical description. Here we describe the reactivity of FeS clusters including environmental effects with quantum mechanical/molecular mechanical (QM/MM) potentials [1] to model Fe-S bare dissociation and substitution reactions in aqueous solution and in protein environments. We show that sextet and quartet spin states cross during bare dissociation in a protein desolvated microenvironment with an homolytic Fe-S bond cleavage mechanism[3]. For water substitution at neutral and acid media, however, no spin-crossings are observed and bond cleavage is heterolytic due to stabilization of the sextet ground state by solvation effects and leaving-group protonation[2,4]. These results help to understand the catalytic mechanisms, stability and biogenesis of iron-sulfur proteins. [1] Ferric-thiolate bond dissociation studied with electronic structure calculations. Arantes GM and Field MJ. J. Phys. Chem. A, 119, 10084-10090, 2015; [2] Modelling the hydrolysis of iron-sulfur clusters. Teixeira MH, Curtolo F, Camilo SG, Field MJ, Zheng P, Li H and Arantes GM. J. Chem. Inf. Model., 60, 653-660, 2020; [3] Homolytic cleavage of Fe-S bonds in rubredoxin under mechanical stress. Arantes GM, Bhattacharjee A, Field MJ. Angew. Chem. Int. Ed., 52, 8144-8146, 2013; [4] Force-induced chemical reactions on the metal centre in a single metalloprotein molecule. Zheng P, Arantes GM, Field MJ e Li H. Nat. Commun., 6:7569, 2015;
Keywords: iron-sulfur clusters, computer simulation, bioinorganic chemistry
Supported by: FAPESP and CNPq

KA.10 - Stability of the Delta variant of SARS-CoV-2 and prediction of mutations that maximize antibody-antigen interaction

Micael Davi Lima de Oliveira [1], Jonathas Nunes da Silva[1], Clarice de Souza Santos[2], João Alfredo Holanda Bessa Neto[2], Rosiane de Freitas[2], Kelson Mota Teixeira de Oliveira[1]
[1]Laboratory of Theoretical and Computational Chemistry, Federal University of Amazonas (Brazil), [2]Institute of Computing, Federal University of Amazonas (Brazil)

The COVID-19 pandemic is of unprecedented impact since the 1918 Spanish flu. The most recent strain of concern of SARS-CoV-2 is Delta (B.1.617.2), responsible for an increase in infections in India and reported with a large increase in viral transmissibility. We studied the stability of the Delta variant mutations. Finally, was performed a computational screening of mutations that maximize the antibody-antigen interaction. We initially performed the stability prediction of the L452R and T478K mutations using the "Residue Scanning" module in the Schrödinger Maestro 2021-2 software. Then, we use the "Affinity Maturation" functionality, whereby the Monte Carlo optimization method we find the mutations that maximize the stability of ACE2-RBD (PDB ID: 6M0J) and antibody-antigen (PDB ID: 7BWJ) binding. Throughout the interpretation of the results, it was considered that the negative sign denotes an increase in stabilization and affinity. We found that the Delta variant L452R mutation achieved stability at -8.161 kcal/mol and affinity of -0.182 kcal/mol for ACE2-RBD. Although the T478K mutation showed a destabilization at +19.490 kcal/mol, it induced an increase in affinity at -5.046 kcal/mol. In this way, we can see an evolution in search of greater structural stability. These values are relatively far from what the virus could actually achieve in terms of stability, where we obtained the maximized value at -96.252 kcal/mol. This, therefore, indicates that SARS-CoV-2 has been seeking marginal stability as a form of adaptation. Regarding the maximization of the antibody-antigen interaction, we found that in terms of stability T333H, A363M, V510I with -33.543 kcal/mol. In terms of affinity, we obtained T333H, V445Q, H519R with -10.501 kcal/mol. Finally, we are currently running molecular dynamics simulations to confirm these conclusions. Therefore, we hope with these results to maximize the effectiveness of the next generation of vaccines so that they are protected against emerging variants.
Keywords: Delta variant, Monte Carlo, SARS-CoV-2. **Supported by:** CNPq