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Explaining station inhibition effectiveness by quantum biochemistry computation

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Hundreds of millions of adults have high cholesterol, which has generated a billionaire market of drugs (mainly statin-based drugs) devised to reduce and control the total serum cholesterol levels. Patents covering the leading statins have expired recently, which pressures the development of new drugs for the market. Statins act by inhibiting the 3-hydroxy-3-methylglutaryl coenzyme (HMG-CoA) reductase in the process of converting HMG-CoA, a committed step in the biosynthesis of cholesterol.

In this work, we take full advantage of the published crystallographic data of HMGR complexed with statins to perform computer simulations within an *ab-initio* quantum mechanical approach, based on the density functional theory (DFT) and in the framework of the molecular fractionation with conjugate caps (MFCC) strategy, to investigate the details of the binding interaction of the statins atorvastatin (A, PDB ID 1HWK), rosuvastatin (R, 1HWL), fluvastatin (F, 1HWI), cerivastatin (C, 1HWJ), mevastatin (M, 1HW8), and simvastatin (S, 1HW9) to the HMGR enzyme. The purpose is to elucidate why statins have differences in their efficiency to reduce cholesterol levels by obtaining and comparing the interaction energy between the HMGR residues and the ligand atoms. The main advantage of the methodology we propose here is the possibility to evaluate which amino acid residues contribute more intensely to the stabilization of the statin-HMGR complex, which canbe very helpful for purposes of drug design and delivery.

Biography

E. L. Albuquerque is a Full Professor at the Department of Biophysics, Universidade Federal do Rio Grande do Norte, in Natal-RN, Brazil. He received his Ph.D. degree in Physics in 1980 from the University of Essex, England. He spent sabbatical leaves, among others, at the International Centre for Theoretical Physics (Trieste-Italy) in 1982, the Centre for Chemical Physics, University of Western Ontario (London-Ont, Canada) in 1991/92, and Harvard University (Cambridge-MA, USA) in 1995/96. He has authored or co-authored over 200 scientific articles, including one book and three review articles.

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