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A NOVEL 7D-QSAR APPROACH, COMBINING QM BASED GRID AND SOLVATION MODELS TO PREDICT HOTSPOTS AND KINETIC PROPERTIES OF MUTATED ENZYMES: AN ENZYME ENGINEERING PERSPECTIVE

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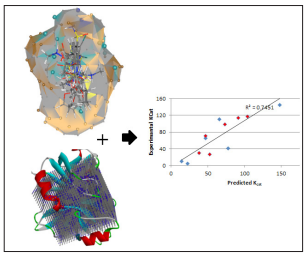
The globalenzyme market was estimated at $7,082 million as of 2017 and is expected to reach $10,519 million in 2024. At a CAGR of 5.7% from 2018 to 2024, enzymes like transaminases are going to contribute the maximum for this growth. Enzymes are molecular machineries used in various industries such as pharmaceuticals, cosmetics; food and animal feed, paper and leather processing, biofuel etc. Nevertheless, this has been possible only by the breath-taking efforts of the chemists and biologists to evolve/engineer these mysterious biomolecules to work the needful. The methodologies for this research include the well-established directed evolution, rational redesign and relatively less established yet much faster and accurate insilico methods. Main agenda of an enzyme engineering project is to derive screening and selection tools to obtain focused libraries of enzyme variants with desired qualities. As a proof of concept, for the first time, receptor dependent 4D Quantitative Structure Activity Relationship (RD-7D-QSAR) to predict kinetic properties of enzymes has been demonstrated by *Pravin Kumar et al*. The methodology was extended to study transaminase. Induced-fit scenarios were explored using QM/MM simulations which were then placed in a grid that stores interactions energies derived from QM parameters (QM grid). The novelty of this study is that the mutated enzymes were immersed completely inside the QM grid and this was combined with solvation models to predict descriptors. After statistical screening of descriptors, QSAR models showed >90% specificity and >85% sensitivity towards the experimental activity. Mapping descriptors on the enzyme structure revealed hotspots important to enhance the enantioselectivity of the enzyme.



7D-QSAR protocol/paradigm to predict enzyme kinetic properties

Biography

Pravin Kumar R has completed his Doctorate in Computational Biology from Bharathiar University, Tamil Nadu, India. He has 15 years of Industrial Experience on different projects pertaining to target deconvolution and enzyme engineering studies. He has 25 international publications, most of it on techniques such as Protein Modelling, Molecular Dynamics, Quantum Mechanics Hybridised with Molecular Dynamics (QM/MM), 4D QSAR, etc. He has developed the Enzyme Engineering Framework which is composed of algorithms and screening protocols of core quantum mechanics, QM/MM and QSAR techniques. The framework can predict hotspots and enzyme variants with better activity (K_{cat}, K_m). This framework was used to engineer transaminase to expand its substrate scope towards bulky ketones. He has participated and given oral presentation in Enzyme Engineering conferences: BIOSIG 2014, Toyama, Japan, BIOSIG 2015 Boston, USA and BIOSIG 2015, Toulouse, France. He holds several positions such as, Bioinformatician in VittalMallya Scientific ResearchFoundation, Bangalore, India Aug ('2004 to Aug' 2007); Team Head of Research in Bioinformaticsat Jigsaw Bio Solutions Pvt Ltd., Bangalore, India (Sep'2007 to Dec'2008); Project head for Computational Biology at Prescient Biosciences Pvt. Ltd, Peenya, Bangalore, India (Jan'2009 to Aug'2010); Team lead and Senior Scientist, in silico, Polyclone Bioservices Pvt Ltd, Jayanagar, Bangalore, India (Oct' 2010 to Aug' 2016) and Director, Quantum Zyme, Bangalore, India from Sep' 2016 to May' 2018. He is the Reviewer of *Journals J. Biomolecular Structure and Dynamics, J. Molecular Catalysis, J. Computational Biology and Chemistry*.

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