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Enabling Drug Discovery in the Cloud with Comparative Genomics

Gerald J. Wyckoff

University of Missouri-Kansas City, USA

Abstract

Using our evolutionary and informatics expertise, we developed methodologies to aid the drug discovery processes. While we initially developed virtual screening technologies for scientists studying the functional effects of variation at the genetic and proteomic level, we began development of a small molecule and protein "fingerprinting" tool to permit the study of chemical spaces divergent from other structure-hopping technologies. We extended our studies to include development of methodologies forportfolio analysis.

For validation,proteins known to interact with Rad52 (PDB:1H2I) were examined. Comparative genomics was essential in aligning structures from divergent species for further analysis. Proteins examined included Rad51, RPA, Rad59 and BRCA. Regions of those compounds that potentially interact near the DNA binding domain were subdivided into "interacting or likely interacting regions" and "non-interacting regions". These regions were then subjected to our fingerprinting methodology, which builds a linear "information signature" relying on fragment geometric and physicochemical properties to search a large pre-generated compound library (20 million compounds). A similarity score was generated and hits ranging from 10-30 were selected for this procedure given fragment length. Compounds were then further selected for size and other RO5 characteristics, generating a list of 10 compounds for further testing. We report the promising results of bench studies on these compounds.

This work has led to research into protein structural alignment tools for target discovery, enabled by cloud computing technologies. We see comparative genomics and proteomics as essential methodologies for bioinformatic work in drug discovery, and explain our validation strategies and future development work.

Biography

Gerald J. Wyckoff is an Associate Professor in Molecular Biology and Biochemistry at UMKC, having completed his Ph.D. at The University of Chicago in Genetics and his B.S. in Biology at Cornell University. His predominant interests are in the application of evolutionary methodologies to the detection of selection in primates and use in drug discovery technologies, and his papers have been published in a range of journals reflecting those interests. He has worked with numerous companies on projects relating to hit-to-lead optimization and primary hit discovery. Separately, he has participated in shaping the new General Education curriculum for Undergraduates at UMKC to help students gain the critical thinking skills necessary for success after graduation. The work presented here has been supported by an NIH STTR grant and private investment.