De novo Design Approaches to Drug Discovery Targeting Tsg101 and nSMase2
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Abstract

Computer-based virtual screening is a proven avenue for drug lead discovery and a recent study has demonstrated that it is possible to screen upwards of 10^14 molecules to a protein target. An orthogonal approach, termed de novo design, aims to grow small organic molecules from scratch which exhibit potent activity toward the identification of more optimal drug-like leads with fewer issues surrounding off-target activity. In this study, we aimed to apply de novo design strategies into the program DOCK. (1) To learn virtual ligand generation (DOCK) from scratch, (2) to simulate receptor binding using genetic algorithm principles starting from either an assembly or a single ligand, (3) to simulate receptor binding using genetic algorithm principles starting from either an assembly or a single ligand. The ultimate goal is to create novel fingerprints of molecules that are physicochemical and favorable interactions. Experimental testing of the best docking poses from the docking experiments with the selected fragment(s) from the de novo design platform. Few molecular constructs were identified for which top scoring molecules are being tested to select suitable databases such as ZINC and PubChem to identify compounds for purchase and experimental testing.

Top 50 Scoring Molecules of each Similarity Score List

Virtual Screening Molecule has Enhanced Binding Interactions

Conclusions and Future Endeavors

• The novel DOCK algorithms were derived, which include de novo design.
• A robust de novo design protocol was created and tested for both refinement and generation.
• We created physicochemically reasonable ensembles of molecules through de novo and de novo design.
• DOCK and DOCK QA successfully explore relevant chemical space while maintaining key binding interactions.
• Currently, we are planning on the next DOCK8 software release which will include the genetic algorithm.

Fitness Convergence through Single Molecule Evolution

Major Binding Sites Identified in Tsg101

De novo Molecules Mimic Reference Footprints

Neutral Sphingomyelinase 2 (nSMase2)

Acknowledgments

Current Collaborations: NW: Jennifer Davis, Indiana; OK: Inna Birken, Indiana, ICL: Victoria Giacomino, Stony Brook, PA: Maryanne Hain, Stony Brook

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