ClusterCAD: a computational platform for type I modular polyketide synthase design

ClusterCAD is a web-based toolkit designed to leverage the collinear structure and deterministic logic of type I modular polyketide synthases (PKSs) for synthetic biology applications. The unique organization of these megasynthases, combined with the diversity of their catalytic domain building blocks, has fueled an interest in harnessing the biosynthetic potential of PKSs for the microbial production of both novel natural product analogs and industrially relevant small molecules. However, a limited theoretical understanding of the determinants of PKS fold and function poses a substantial barrier to the design of active variants, and identifying strategies to reliably construct functional PKS chimeras remains an active area of research. In this work, we formalize a paradigm for the design of PKS chimeras and introduce ClusterCAD as a computational platform to streamline and simplify the process of designing experiments to test strategies for engineering PKS variants. ClusterCAD provides chemical structures with stereochemistry for the intermediates generated by each PKS module, as well as sequence- and structure-based search tools that allow users to identify modules based either on amino acid sequence or on the chemical structure of the cognate polyketide intermediate. ClusterCAD can be accessed at https://clustercad.jbei.org and at http://clustercad.igb.uci.edu.