Coordinate Descent in Two Dimensions for Protein Loop Closure

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This study proposes a novel algorithm inspired by CCD which varies each pair of backbone dihedral angles in each amino acid simultaneously; essentially performing 2-dimensional CCD. Upon testing on 5 different loops, the algorithm was shown to be on average 2.5 times faster than CCD. Knowledge of a protein's structure is crucial to understanding its biological function especially its role in disease. In proteins, loop regions, which join semi-rigid segments of alpha-helices and beta-sheets, play a crucial role in intermolecular interactions, such as the binding of an antibody to an antigen (Feller and Lewitsky 2012). In protein structure prediction from homologous structure templates, loops often contain insertions or deletions of sequence and therefore need to be modeled using de novo methods based on the amino acid sequence. One crucial step in loop modeling is loop closure, which focuses on ensuring that the predicted loop structure connects the two adjoining regions. The cyclic coordinate descent (CCD) algorithm, originally developed for addressing inverse kinematics problems, was implemented by Canutescu and Dunbrack to address this fundamental loop modeling problem (Canutescu and Dunbrack 2003). The original CCD involved optimizing one dihedral angle at a time to superimpose the mobile C-terminal atoms onto the corresponding anchor C-terminal atoms. The CCD algorithm is currently the main algorithm in use for loop closure in a variety of molecular modeling programs. Since each amino acid consists of two flexible dihedral angles, the novel approach is more efficient because it reduces the total number of calculations and takes advantage of known Ramachandran probability maps to limit potential backbone dihedral angle pairs to only those naturally observed.

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