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Density-cluster NMA: A new protein decomposition technique for coarse-grained normal mode analysis

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Normal mode analysis has emerged as a useful technique for investigating protein motions on long time scales. This is largely due to the advent of coarse-graining techniques, particularly Hooke's Law-based potentials and the rotational–translational blocking (RTB) method for reducing the size of the force-constant matrix, the Hessian. Here we present a new method for domain decomposition for use in RTB that is based on hierarchical clustering of atomic density gradients, which we call Density-Cluster RTB (DCRTB). The method reduces the number of degrees of freedom by 85–90% compared with the standard blocking approaches. We compared the normal modes from DCRTB against standard RTB using 1–4 residues in sequence in a single block, with good agreement between the two methods. We also show that Density-Cluster RTB and standard RTB perform well in capturing the experimentally determined direction of conformational change. Significantly, we report superior correlation of DCRTB with *B*-factors compared with 1–4 residue per block RTB. Finally, we show significant reduction in computational cost for Density-Cluster RTB that is nearly 100-fold for many examples.