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Coarse-graining protein energetics in sequence variables FEI ZHOU, GEVORG GRIGORYAN, AMY KEATING, Departments of Biology, MIT, GERBRAND CEDER, Departments of Materials Science and Engineering, MIT, DANE MORGAN, Department of Materials Science and Engineering, University of Wisconsin - Madison — We show that cluster expansions (CE), previously used to model solid-state materials with binary or ternary configurational disorder can be extended to the protein design problem. We present a generalized CE framework, in which properties such as energy can be unambiguously expanded in the amino-acid sequence space. The CE coarse grains over non-sequence degrees of freedom (e.g., side-chain conformations) and thereby simplifies the problem of designing proteins, or predicting the compatibility of a sequence with a given structure, by many orders of magnitude. The CE is physically transparent, and can be evaluated through linear regression on the energies of training sequences. [PRL 95, 148103 (2005)]. We show, as example, that good prediction accuracy is obtained with up to pairwise interactions for a coiled-coil backbone, and that triplet and/or quadruplet interactions are important in the energetics of the more globular zinc-finger and WW domain backbones. In the coiled-coil system, where experimental data is available, the calculated pair interaction parameters compare favorably with measured coupling energies. The clear advantage of a CE driven optimization over a direct one is demonstrated by searching for low-energy sequences on the zinc-finger backbone. Other possible applications of our approach are also discussed.

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