

## Modeling Protein Crystal Growth Through Helical Pseudosymmetry

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Proteins crystallize when their energetically preferred contacts hold them in lattice symmetry. Molecules in adjacent unit cells must have identical orientation. How this rotational restriction arises from the visceral asymmetry of proteins is a key question with implications for improved crystal growth, engineering, and structure determination. Here we consider the process of lattice nucleation and the key role of pseudosymmetry. Pseudosymmetry is observed in many mature crystals, often causing challenges to structure determination including space group ambiguity, and is hypothesized to be a general nucleation intermediate.

If an asymmetric protein has two surface sites X and Y, not too close together, that form a favorable contact, the proteins will tend to form helical chains. If the contact is tight, the helices will be rigid and can associate to form aggregates with some geometric precursors of lattice symmetry. To proceed toward crystalline order, helices must in general be straightened, and their twist angles per subunit must be brought to space-group-compatible values of 0, 60, 90, 120 or 180 degrees. These rearrangements of the native helix require energy for the distortion of either the protein or the contact or both. If additional contacts have favorable strength and geometry, they can provide sufficient energy to rectify the helices and produce a lattice whose continued growth is then energetically favored.

We have modeled these processes in several well-studied protein crystals, using 3-D graphics to visualize the stepwise development of the lattice. The work leads to several interesting predictions for the arrangements of contacts in mature lattices and for the patterns of pseudosymmetry that are commonly observed in protein crystals.