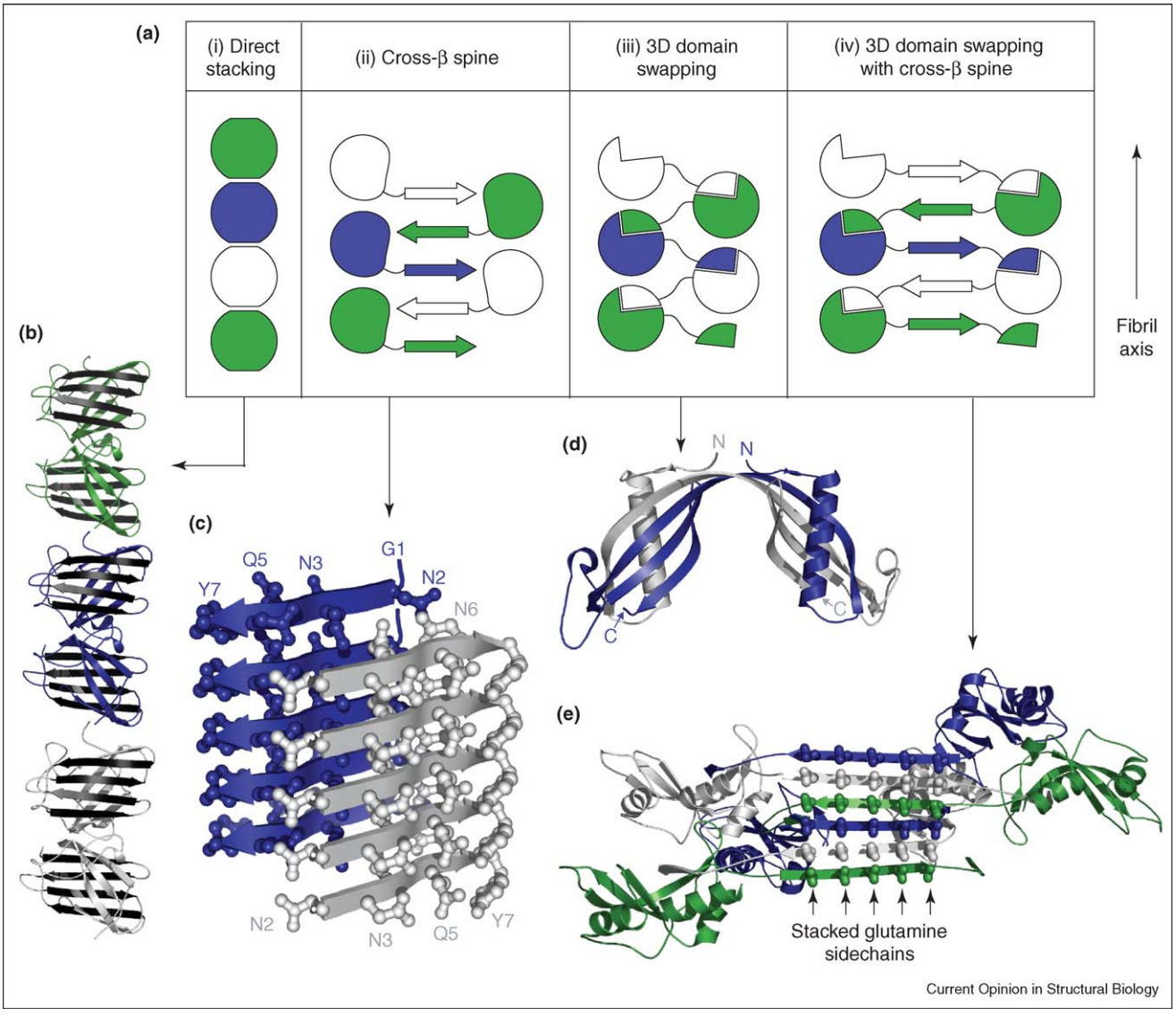
**Figure 2**




Gain-of-interaction models. **(a)** Cartoon depicting the four subtypes of gain-of-interaction models. In direct stacking models (panel i), the gained interaction is achieved via simple stacking of subunits. Alternatively, in the cross-β spine models (panel ii), a segment of the protein separates from the core domain to stack into a cross-β spine, with the core domain decorating the edges of the spine. In the somewhat more elaborate model shown in panel iv, the molecules at the edges of the spine domain swap with identical molecules. This permits a wider range of stable geometries around the cross-β spine. In the remaining subtype (panel iii), proteins first domain swap and then stack into the fibril. **(b)** Ribbon diagram showing a crystalline filament of human superoxide dismutase mutant S134N (PDB code 1OZU [39]). Three dimers stack in an example of a direct stacking model. The β-strands highlighted in black are arranged roughly perpendicular to the fibril axis. **(c)** Ribbon diagram showing the pair of sheets of the GNNQQNY cross-β spine, with backbones represented by arrows and sidechains by ball-and-stick structures (PDB code 1YJP [21••]). The asparagine and glutamine sidechains facing into the space between the two sheets (N2, Q4, N6) pack to form a steric zipper. **(d)** Ribbon diagram showing the crystal structure of a 3D domain-swapped dimer of human cystatin C (PDB code 1G96 [46]). The monomers are colored blue and light gray, to highlight the swapped domains. N and C termini are indicated. **(e)** Ribbon diagram showing one sheet of the 3D domain-swapped cross-β spine model of fibrillar polyglutamine mutants of RNase A [45••]. The view shows one face of the proposed steric zipper, with aligned stacks of glutamine sidechains (shown as sticks) forming hydrogen bonds along the length of the fibril.

have helped to define the structures of the fibrils. There is general agreement that Aβ(1–40) and Aβ(1–42) peptides stack parallel and in register to form a set of β-sheets, with the N-terminal ~10 amino acids being poorly structured. Less clear are the boundaries of the core β-strand and turn regions, as the various studies seem to give conflicting results. The solid-state NMR studies [26,33–36] confer the most constraints on the structure and suggest that a bend in the chain (residues 25–29) brings two β-strands (residues 12–24 and 30–40) into proximity.