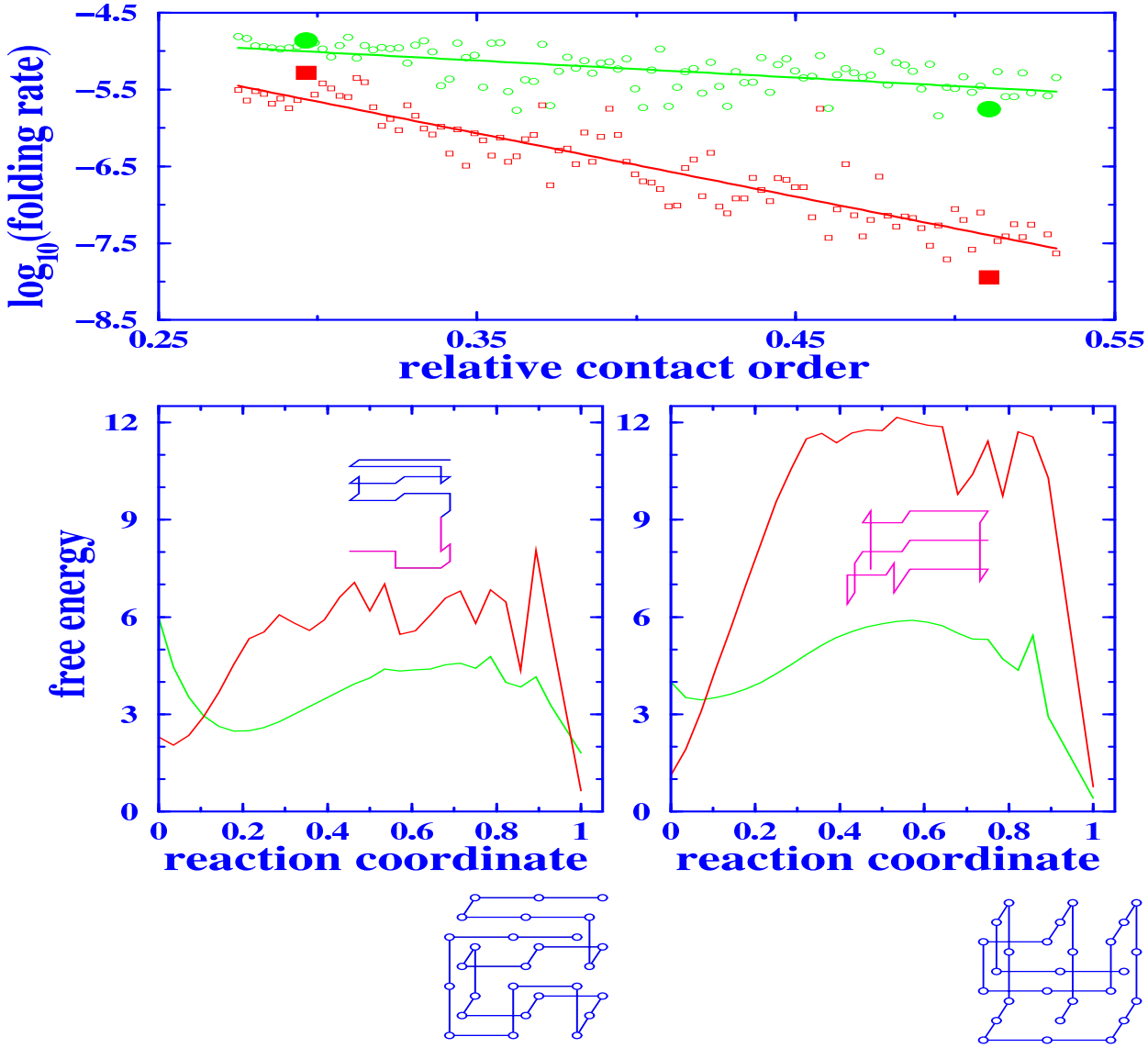

Caption: Local-nonlocal coupling leads to high free energy barriers in the folding of high-contact-order protein structures. The upper panel is logarithmic folding rate vs. relative contact order (CO). Here the common Gō potential (green datapoints) is compared with a potential that entails local-nonlocal coupling (red datapoints). One low-CO structure and one high-CO structure (shown as blue bead-and-stick drawings below the lower panels) are chosen for further illustration. Their folding rates are highlighted by the filled datapoints in the upper panel. They fold at similar speeds (c.f. green filled circles) under the pairwise additive Gō potential, but their folding rates diverge significantly under the local-nonlocal cooperative interaction scheme (c.f. red filled squares). These differences in folding kinetics are consistent with their respective free energy as a function of reaction coordinate Q. (The model protein becomes more native as $Q \to 1$.) Their free energy profiles are shown in the lower panels and are quite similar for the Gō potential (green curves), but the local-nonlocal coupling mechanism (red curves) raises the transition-state barrier of the high-CO structure (lower right panel) far more than that of the low-CO structure (lower left panel). An example transition-state structure is shown for each case in the lower panels. The barrier of a high-CO structure is raised more by local-nonlocal coupling because local conformations are not nativelike for many of its would-be transition-state structures, i.e., structures with intermediate numbers of native contacts. For instance, the magenta structure on the right has 16 native contacts but all of its local conformation are nonnative. This structure would be highly unstable when local-nonlocal coupling is in effect. In contrast, for low-CO structures, substantial parts of many would-be transistion-state structures are locally nativelike. This is illustrated by the structure shown on the left: It has 16 native contacts, the deep blue part is locally nativelike whereas the magenta part is locally nonnative. Such a structure is destablized less by the local-nonlocal coupling mechanism than the all-magenta structure on the right. It is suggested that a similar mechanism is at work in real, small single-domain proteins. See Kaya and Chan, Figure 2, page 527.