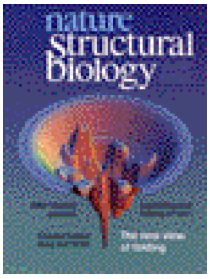
The Folding Funnel and the Rugged Energy Landscape

Images from Dill and Chan, Nature Structural Biology, 1997 http://www.dillgroup.ucsf.edu/

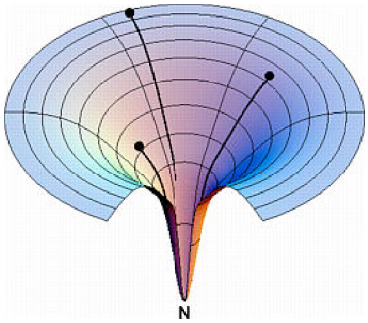


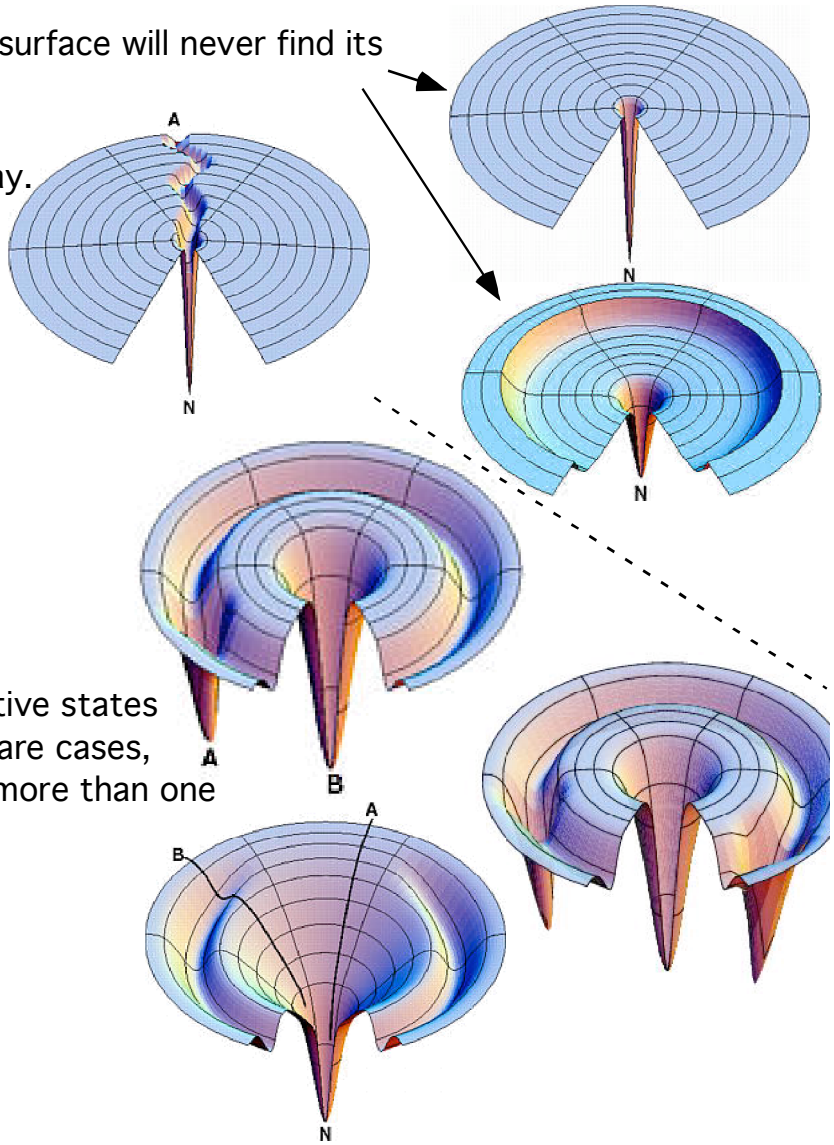
Plots represent 3-dimensional idealizations of a the many, many-dimensional space representing the energy of a protein chain as a function of conformation, under conditions where the native conformation ("N") is most stable (i.e. folding conditions). The energy surfaces correspond to different possible mechanisms for protein folding.

<u>Levinthal paradox:</u> A ball dropped on this surface will never find its way to the hole. Entropic trap.

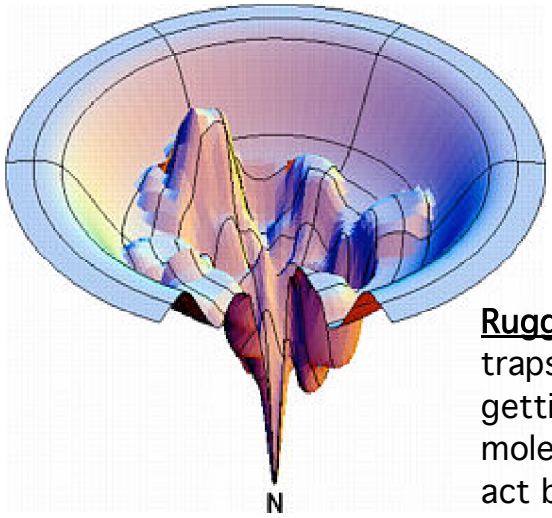
<u>Fixed pathway:</u> One unique folding pathway.

<u>Folding funnel:</u> Many starting conformations rapidly collapse to the native structure.





<u>Moats and traps:</u> Easily accessible non-native states slow down access to the native state. In rare cases, A and B can be of comparable depth and more than one state may be accessible (prion diseases).



<u>Rugged energy landscape:</u> Lots of funnels, moats, and traps -- most of the time required for folding is spent getting out of misfolded states. There are always a few molecules that fold nearly instantaneously. Chaperones act by unfolding the misfolded states.