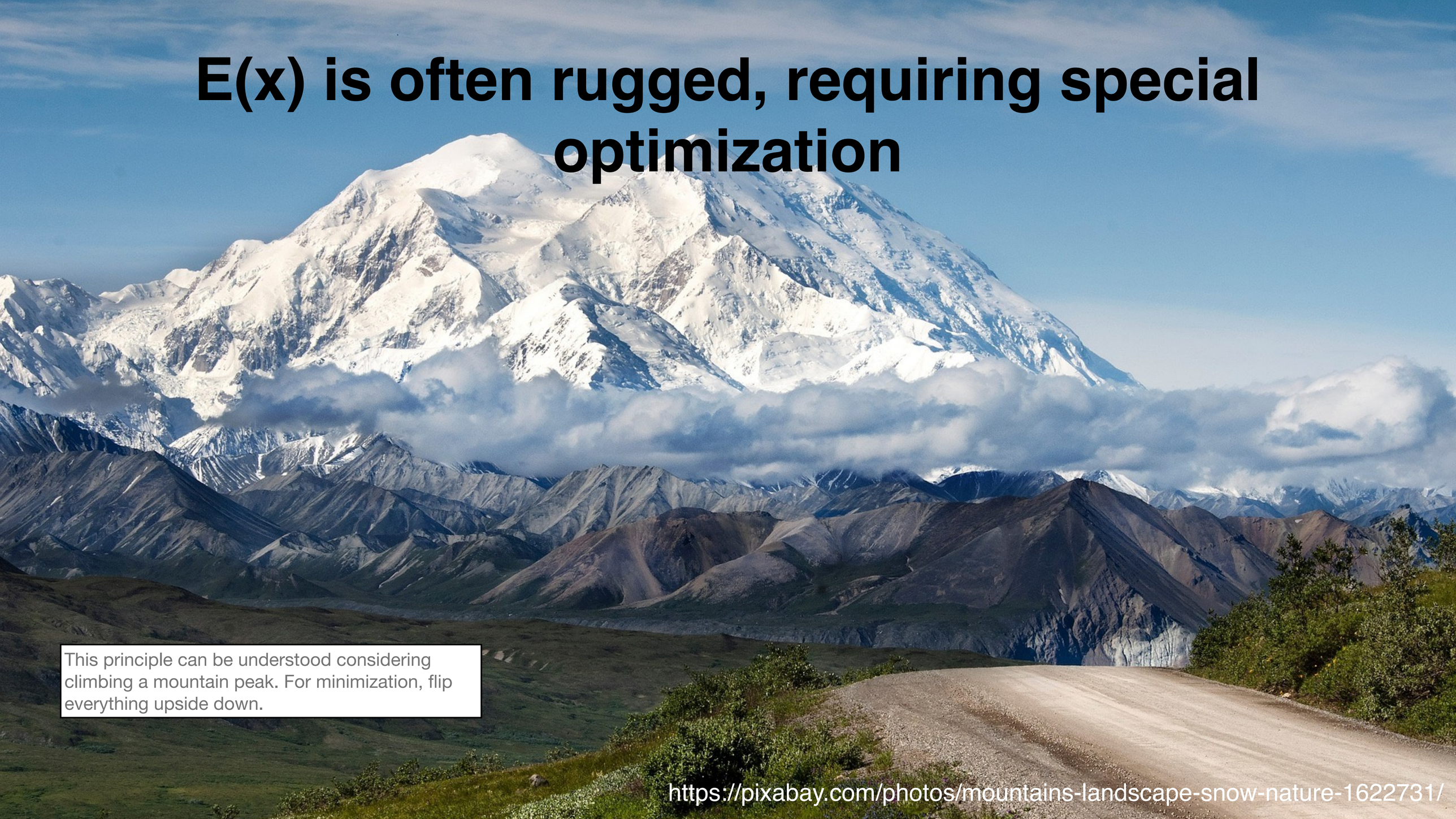
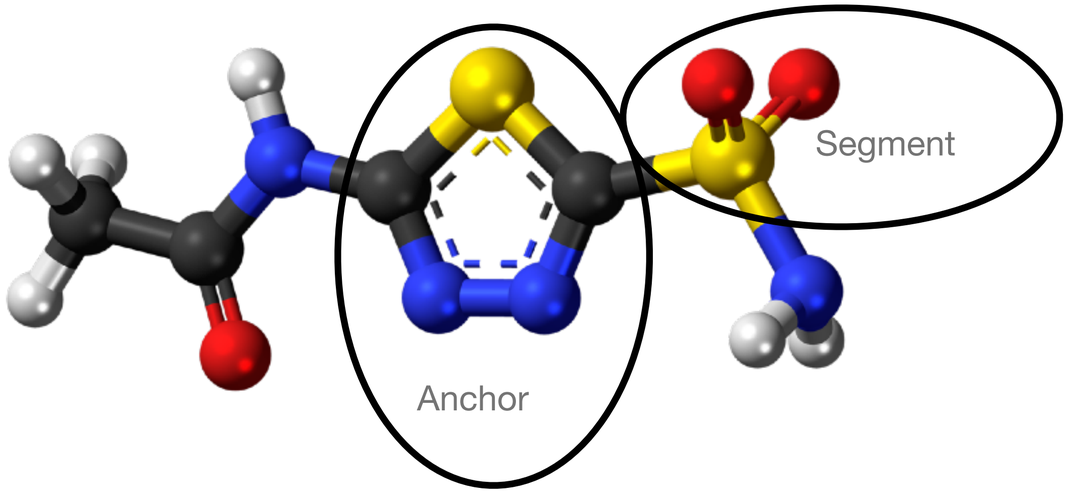
E(x) is often rugged, requiring special optimization



This principle can be understood considering climbing a mountain peak. For minimization, flip everything upside down.

https://pixabay.com/photos/mountains-landscape-snow-nature-1622731/

UCSF DOCK is based on anchor-and-grow



- Receptor spheres and rigid “anchor” in ligand
  - represented as graph of atoms separated by distances
  - docking is search for isomorphic subgraph
- Until the molecule is complete, segments are iteratively
  - added to the anchor and
  - pruned if the energy is too high
- Complete structures are locally minimized