What are alchemical pathways?

- Alchemical pathways are a series of thermodynamic states where intermediate states do not necessarily model a physical system. For example,
  - a drug lead can be morphed into a similar proposed compound
  - harmonic restraints can be added to keep atoms in a certain position
  - states whose energy is a linear interpolation between states 0 and 1 can be defined as, $U_\lambda(r^N) = (1-\lambda)U_0(r^N) + \lambda U_1(r^N)$

Why do we use alchemical pathways?

- Adjacent states along an alchemical pathways have high *configuration space overlap*
- Using alchemical pathways is valid because thermodynamic functions like the Gibbs free energy are *state functions*
  - they only depend on the final values, not the path between them
    - height, weight, coordinates are other state functions
  - Hess' law is based on this property of the Gibbs free energy
- Binding free energy calculations usually involve connecting *alchemical pathways* in a *thermodynamic cycle* that joins the end states of interest