Electrostatics and other interactions in proteins & water

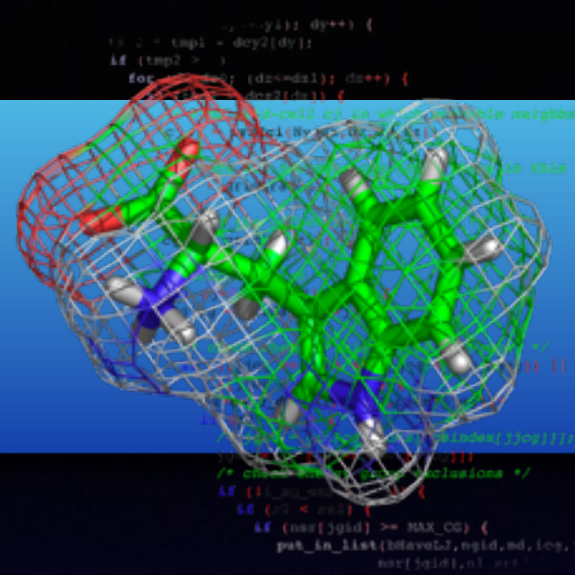
Magnus Andersson

magnus.andersson@scilifelab.se

Theoretical & Computational Biophysics

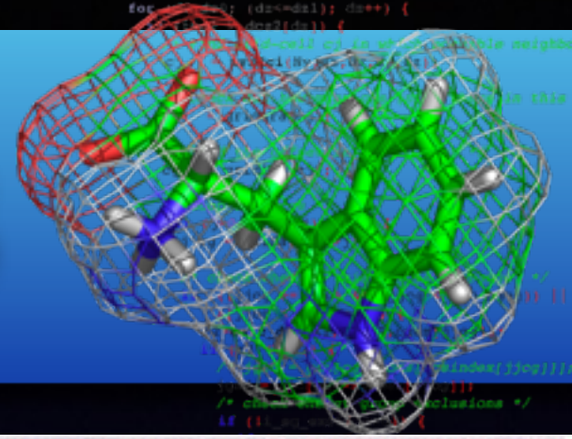

DIGITAL EQUIPMENT CORPORATION

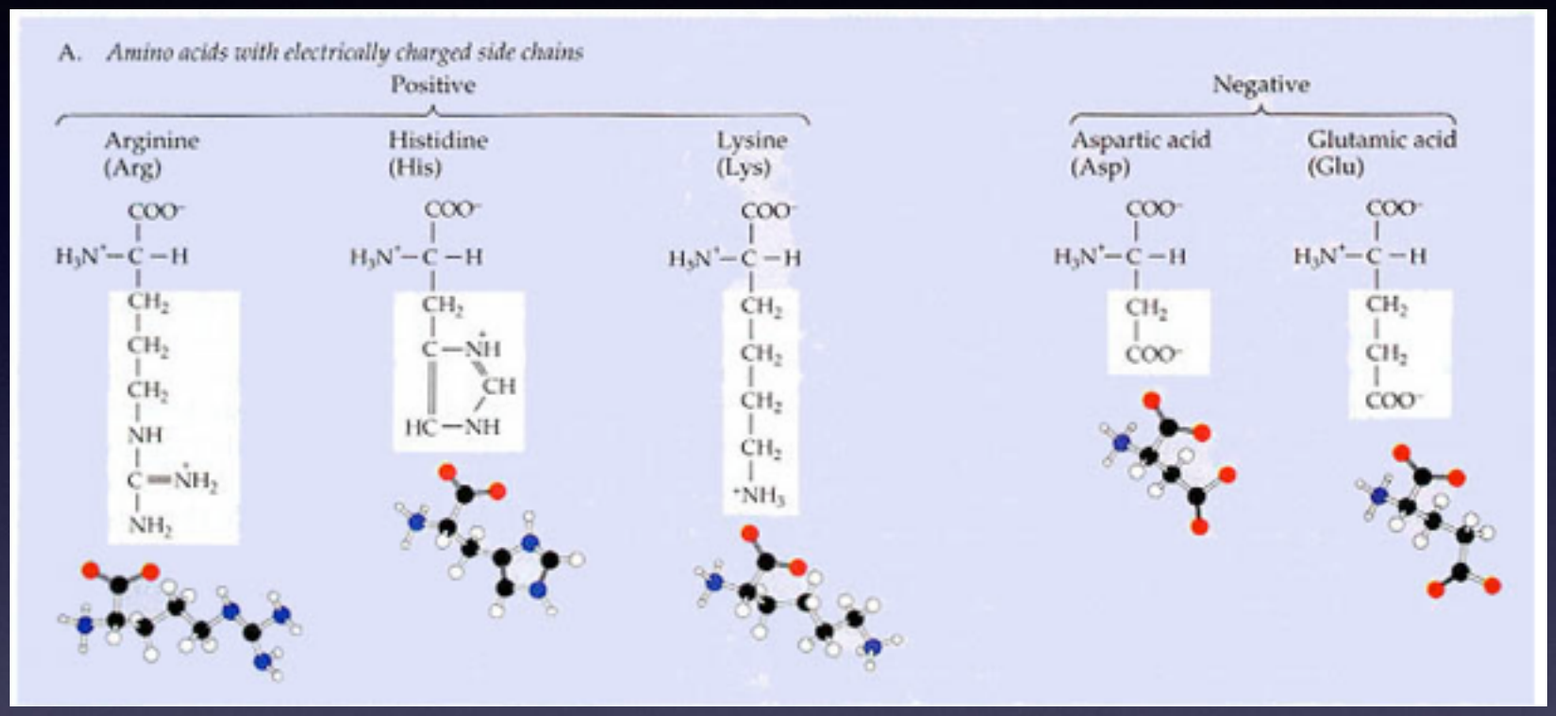
Recap

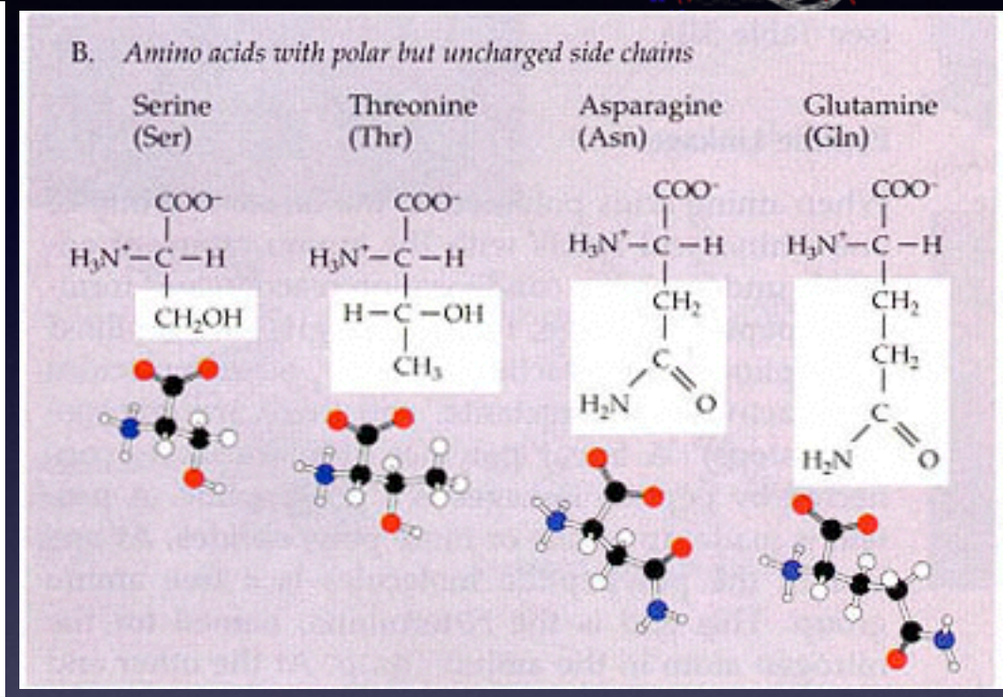


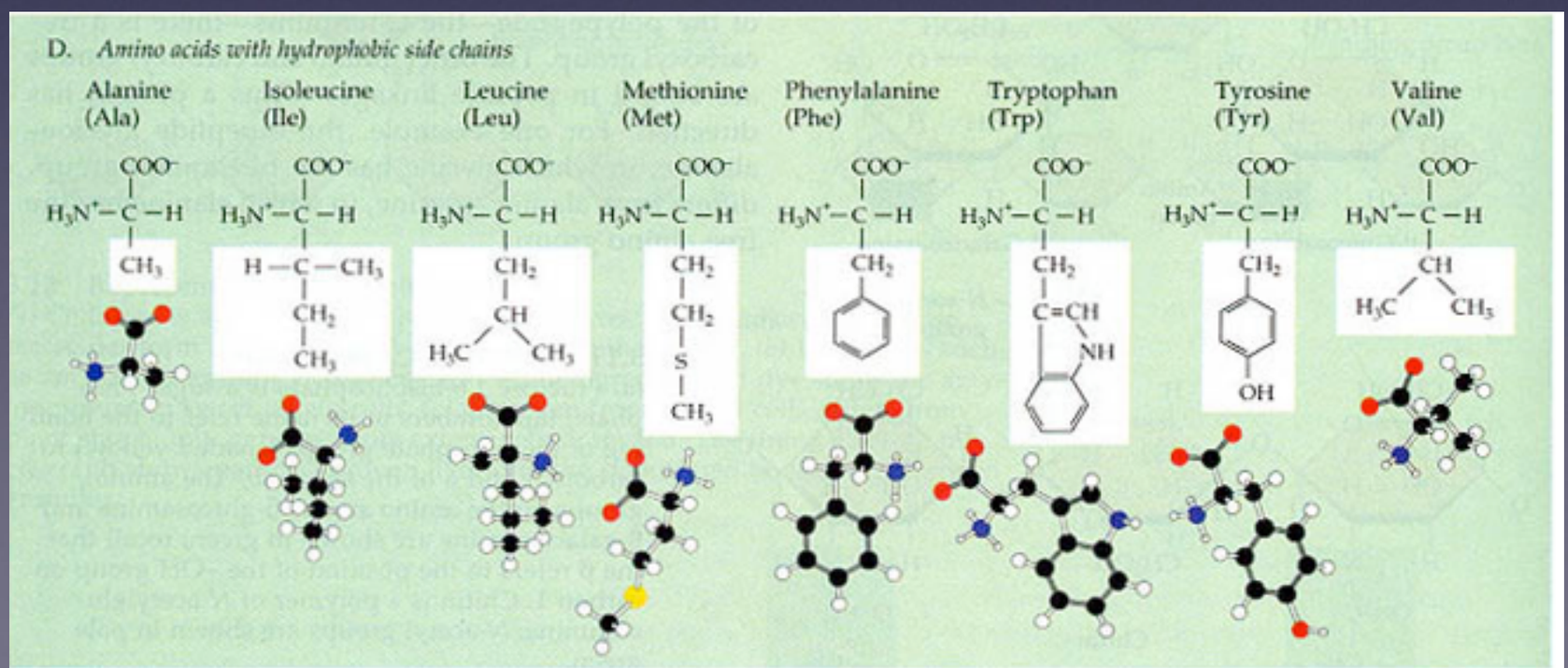
- Amino acids, peptide bonds
- Φ,Ψ torsion set conformational space for a chain (Ramachandran plot)
- determined by side-chain characteristics
- Anfinsen's hypothesis
- Levinthal's paradox
- Secondary structure elements

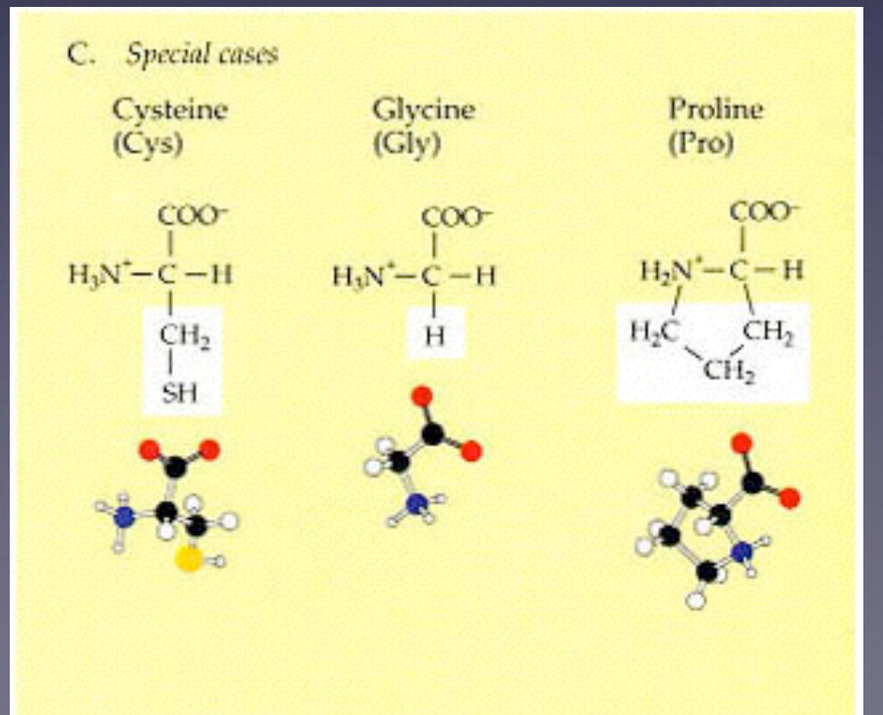
Natural amino acids



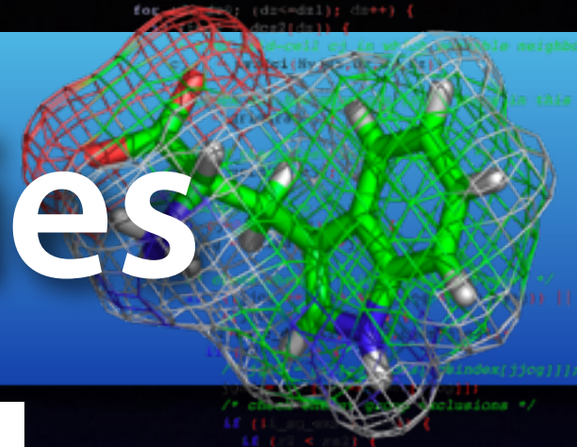


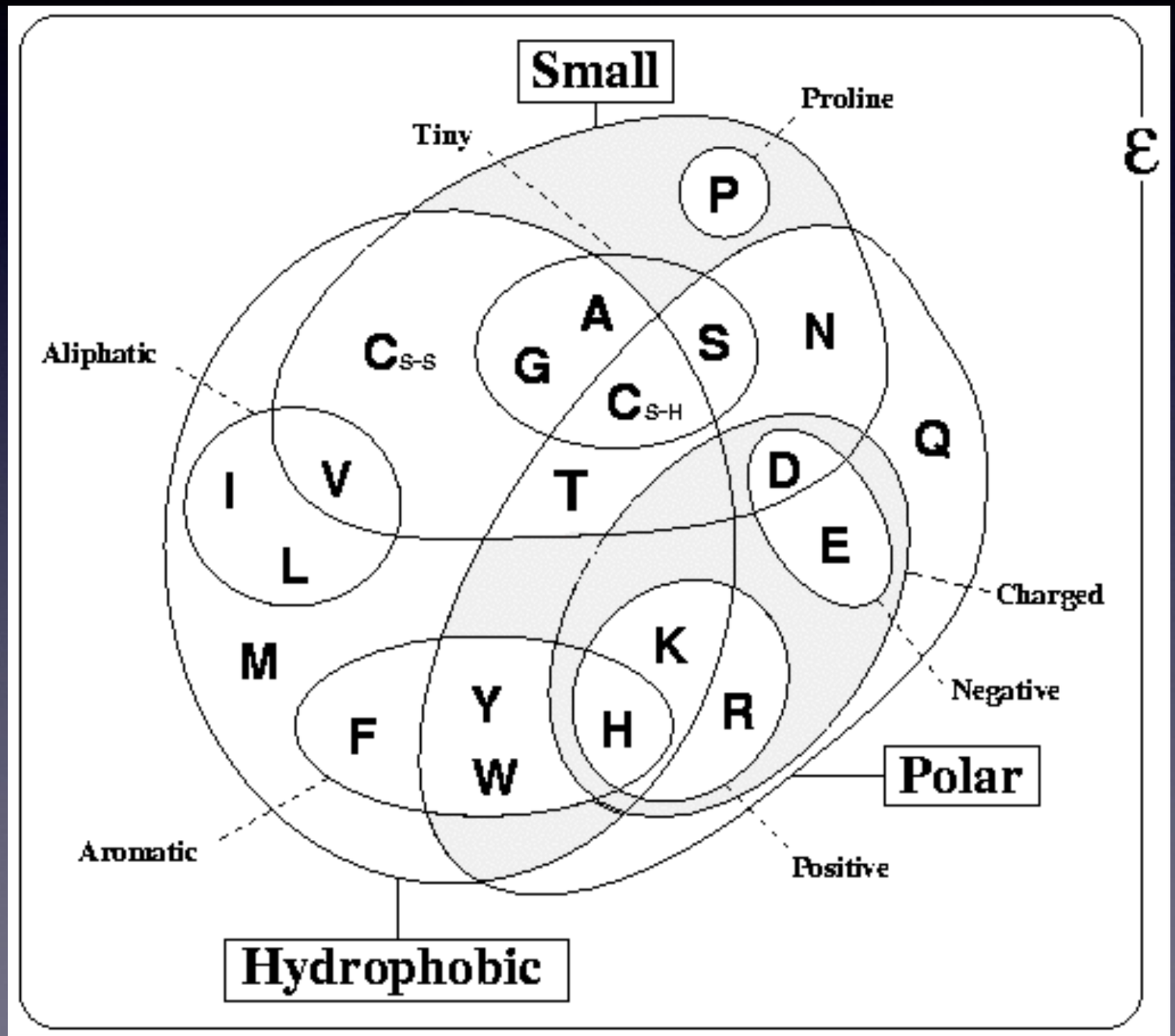






Amino acid properties

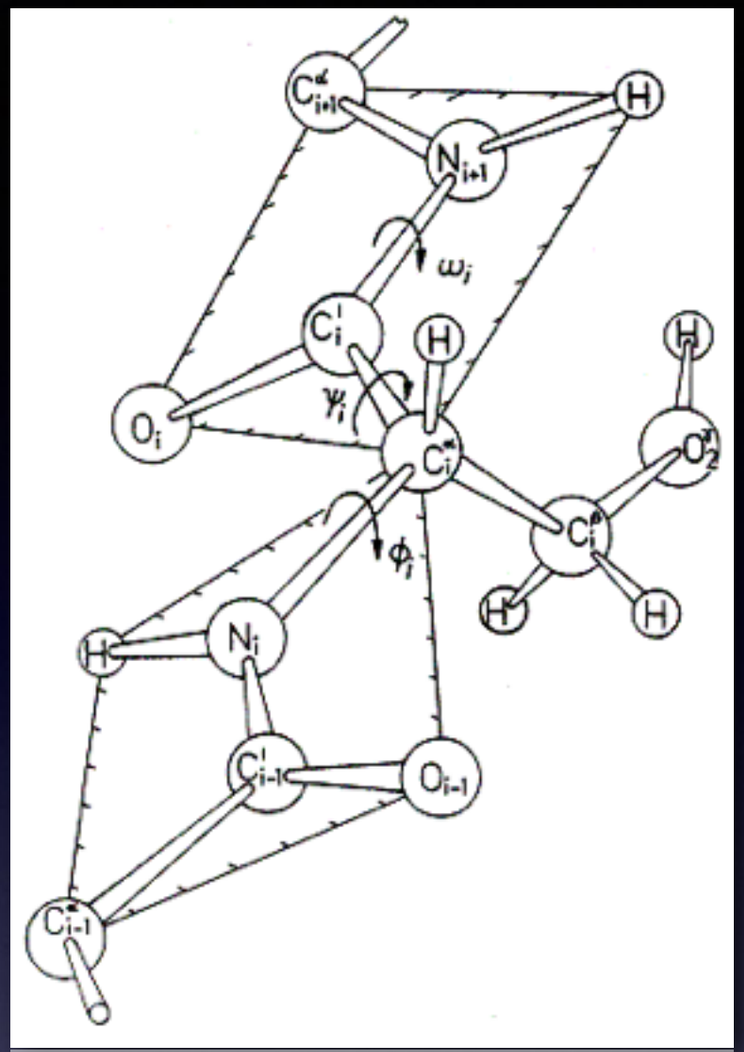


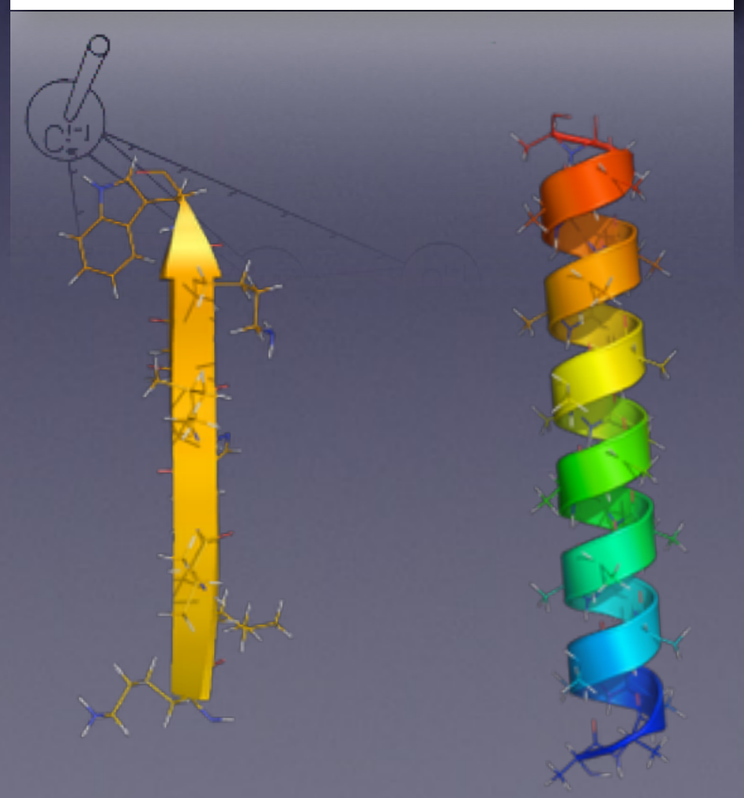


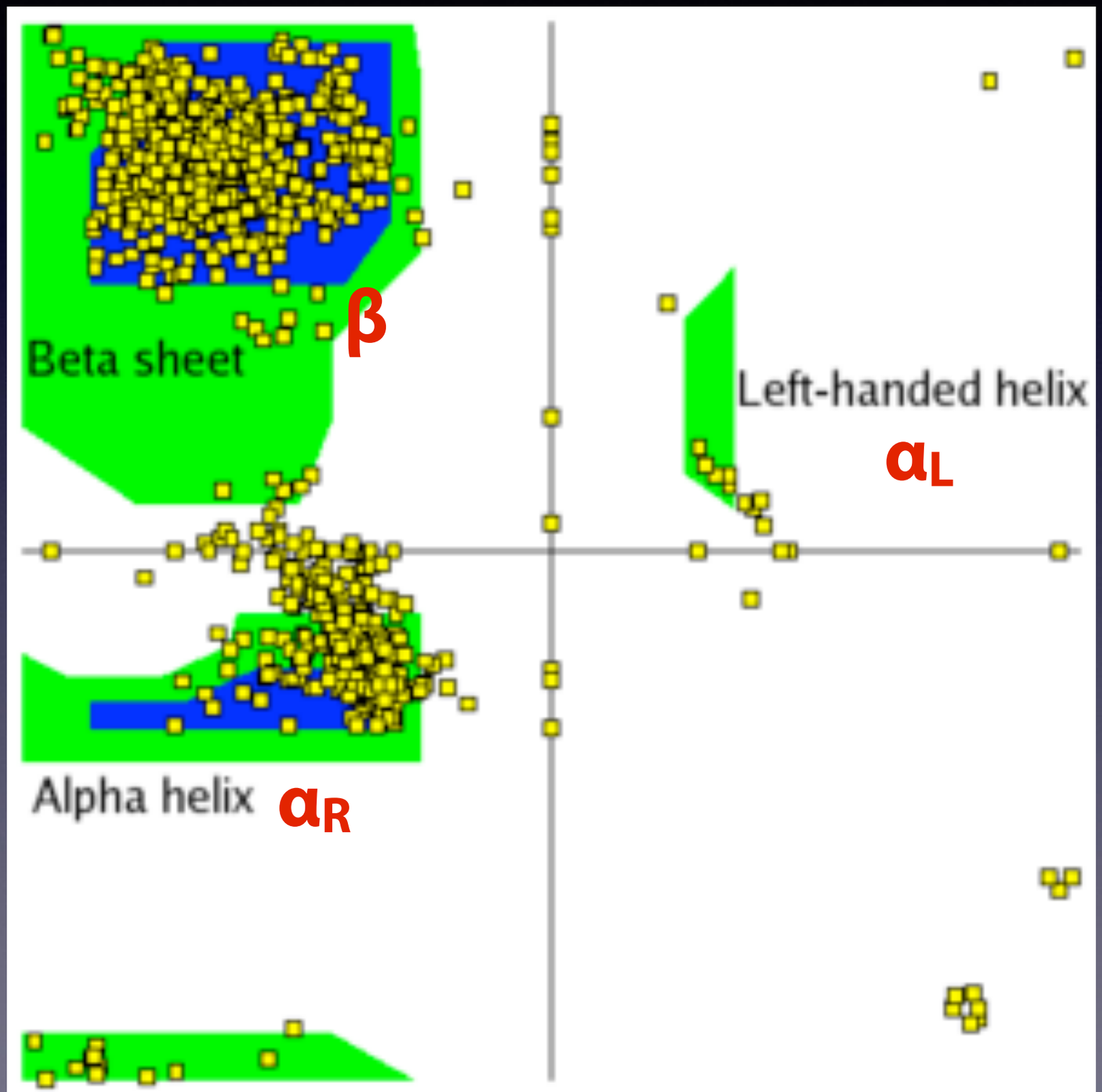
Peptide bond

Dipeptide

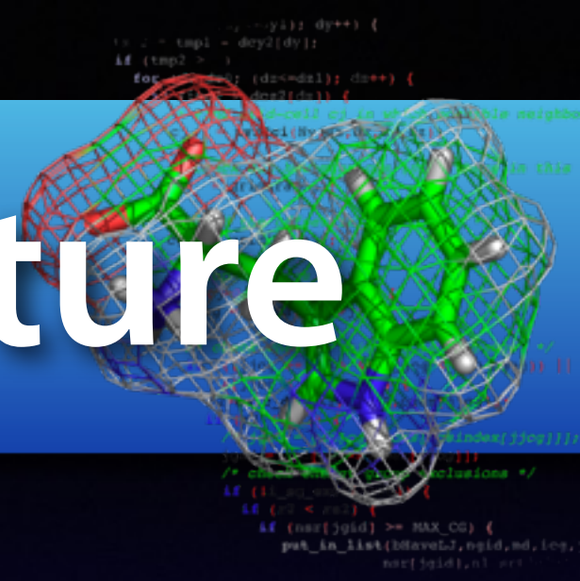
Water


C^{α}_{i+1}
H
N_{i+1}
ω_i
C'_i
H
O_i
ψ_i
C^{α}_i
O'_2
ϕ_i
C^{β}_i
H
H
H
N_i
C'_{i-1}
O_{i-1}
C^{α}_{i-1}


C'_{i-1}

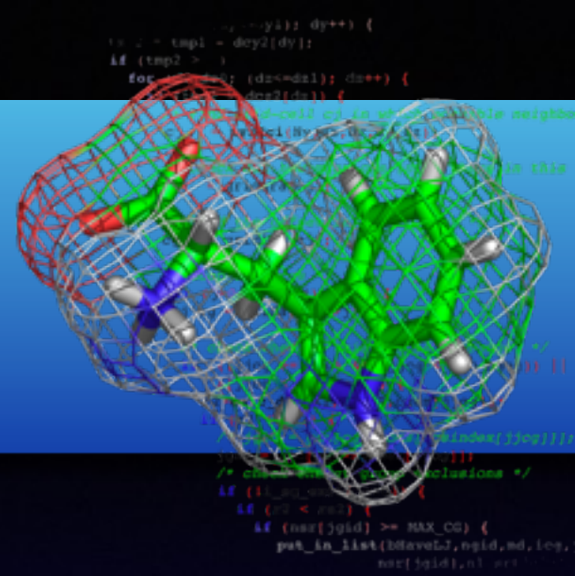

Beta sheet
β
Left-handed helix
α_L
Alpha helix
α_R

Amino acids & structure



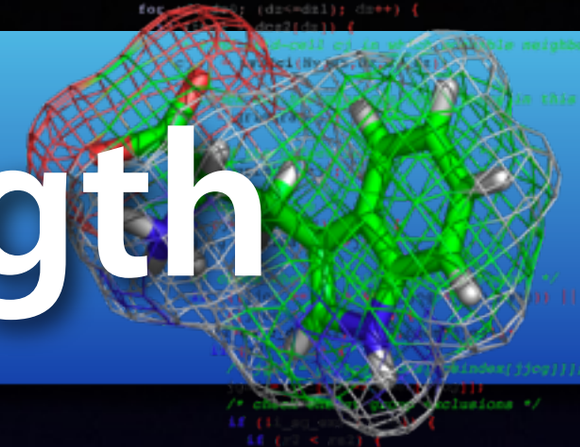
- Proline is very rare in alpha helices
- Glycine is common in tight turns
- Some residues common at helix ends
- Differences inside/surface of proteins

Outline today



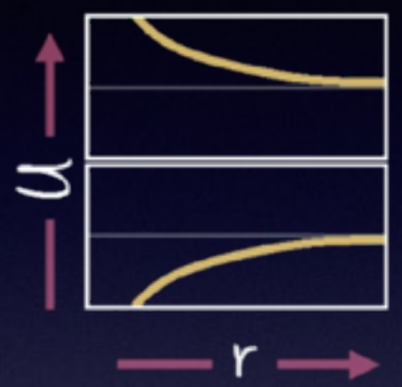
- Semi-empiric modeling (describe interactions)
- Hydrogen bonds & hydrophobic effect
- Boltzmann distribution
- Definitions of entropy, temperature, etc.

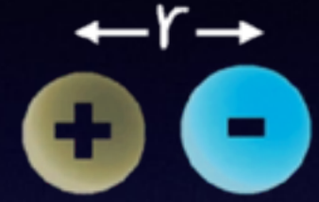
Electrostatic strength



$$+\sum 332 q_i q_j / r$$

All partial charges

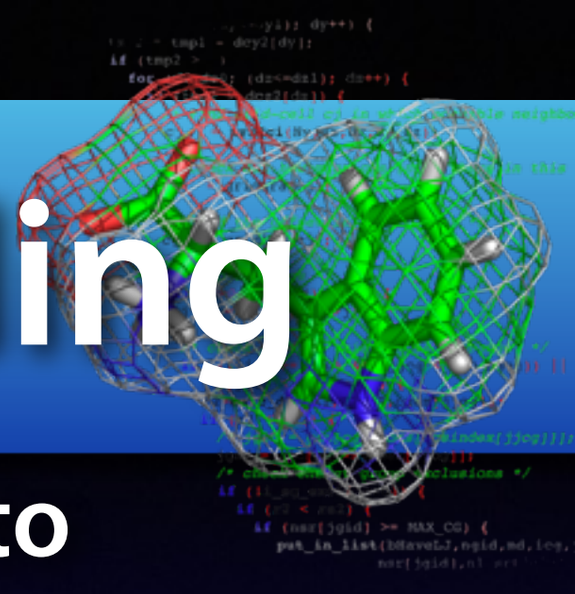




Electrostatic interactions decay as 1/r (slow!)

Example interaction energy:
Two charges separated by ~1Å: 330 kcal/mol!
(Compare to bond rotation, 2-4 kcal)

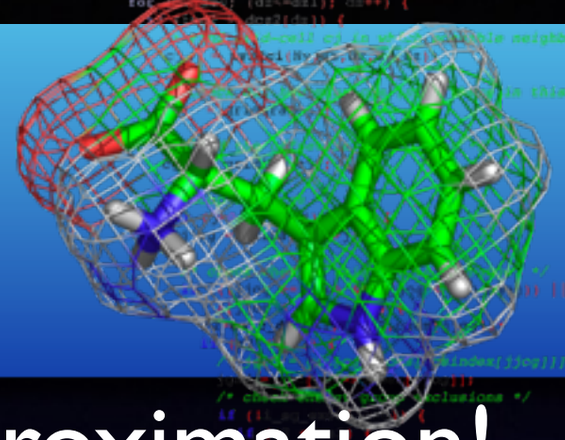
Semi-Empiric Modeling



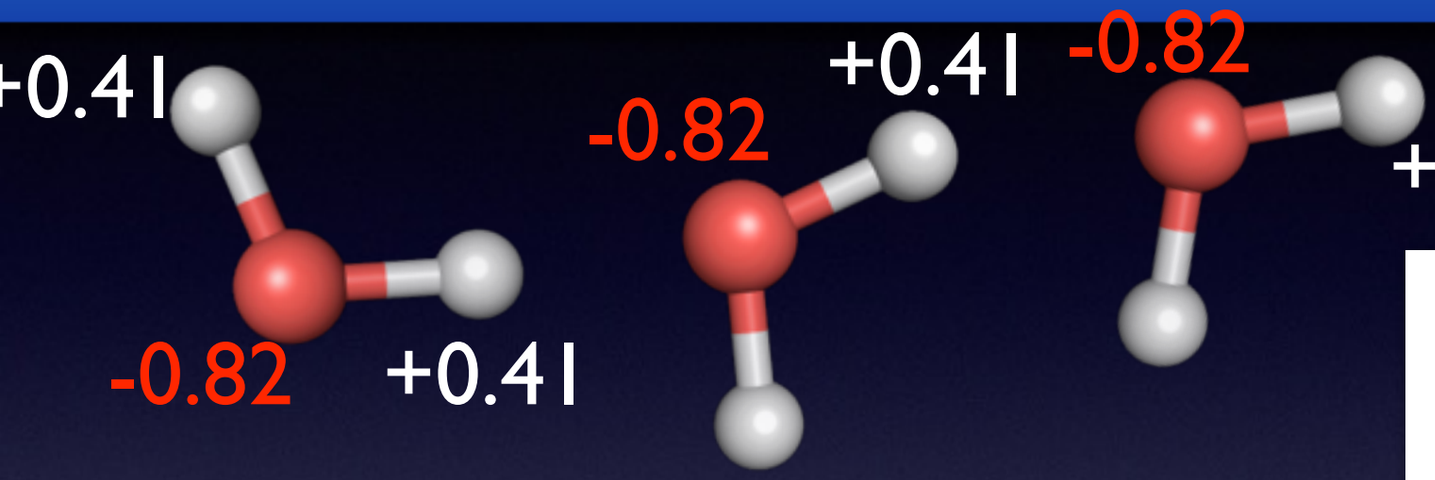
- Use simple interactions, but fit them to reproduce experimental properties
- Compare to Ab initio: Use physics, and extrapolate 10-15 orders of magnitude
- Arieh Warshel, Martin Karplus, Michael Levitt

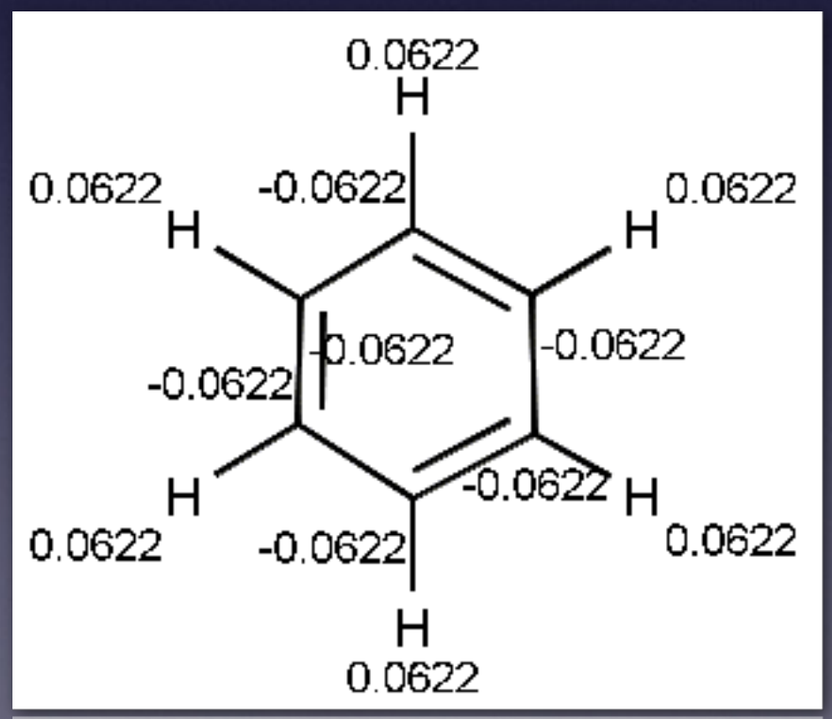
Nobel Prize Chemistry 2013

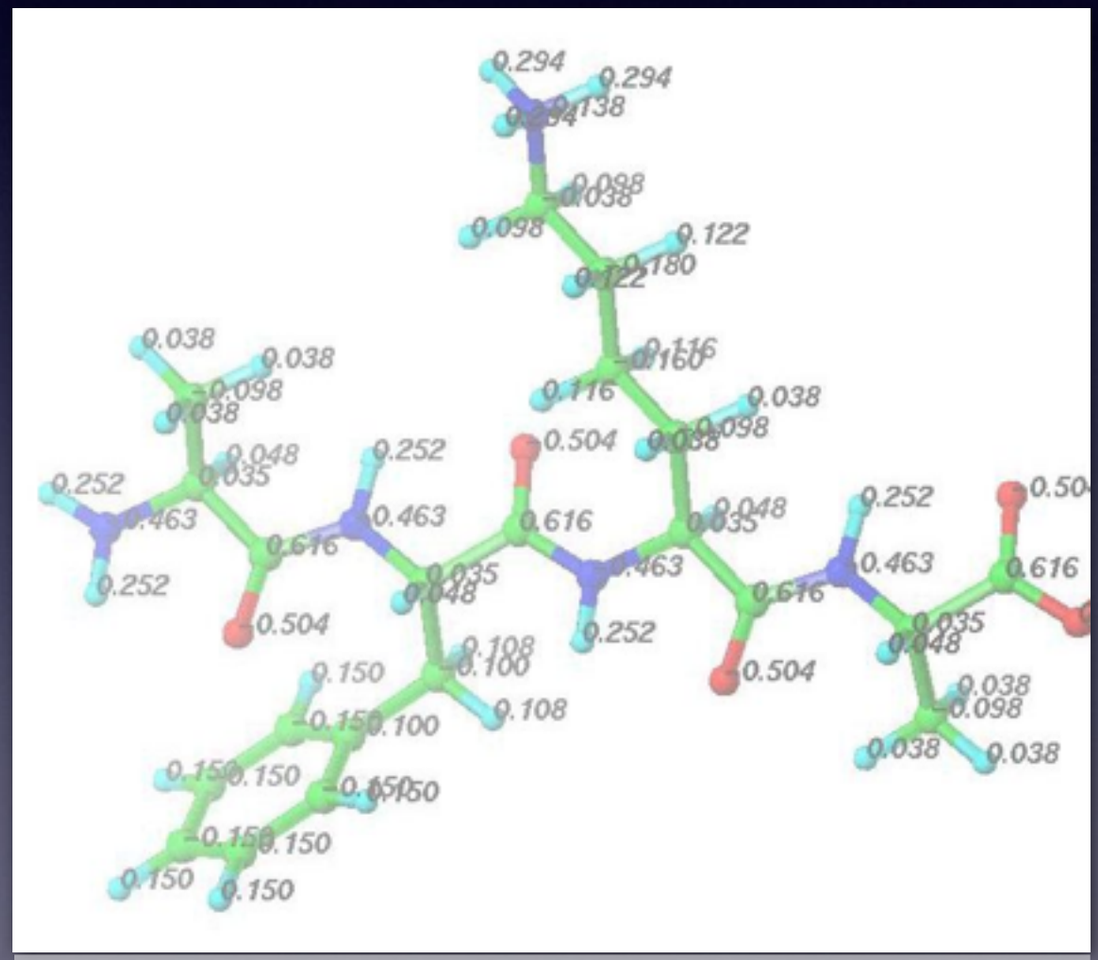
Partial charges



Approximation!

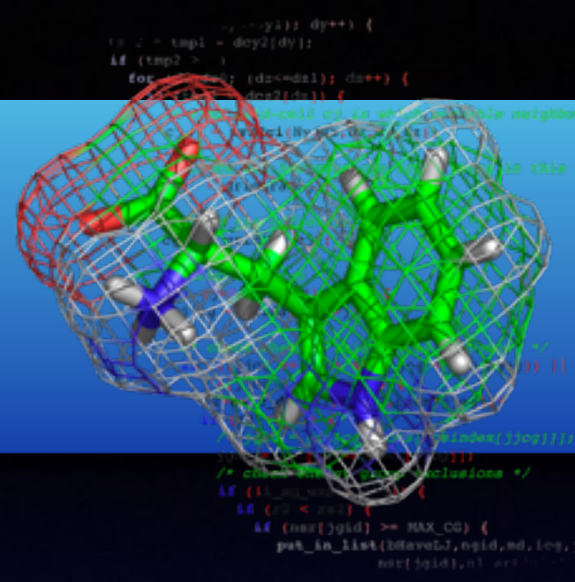


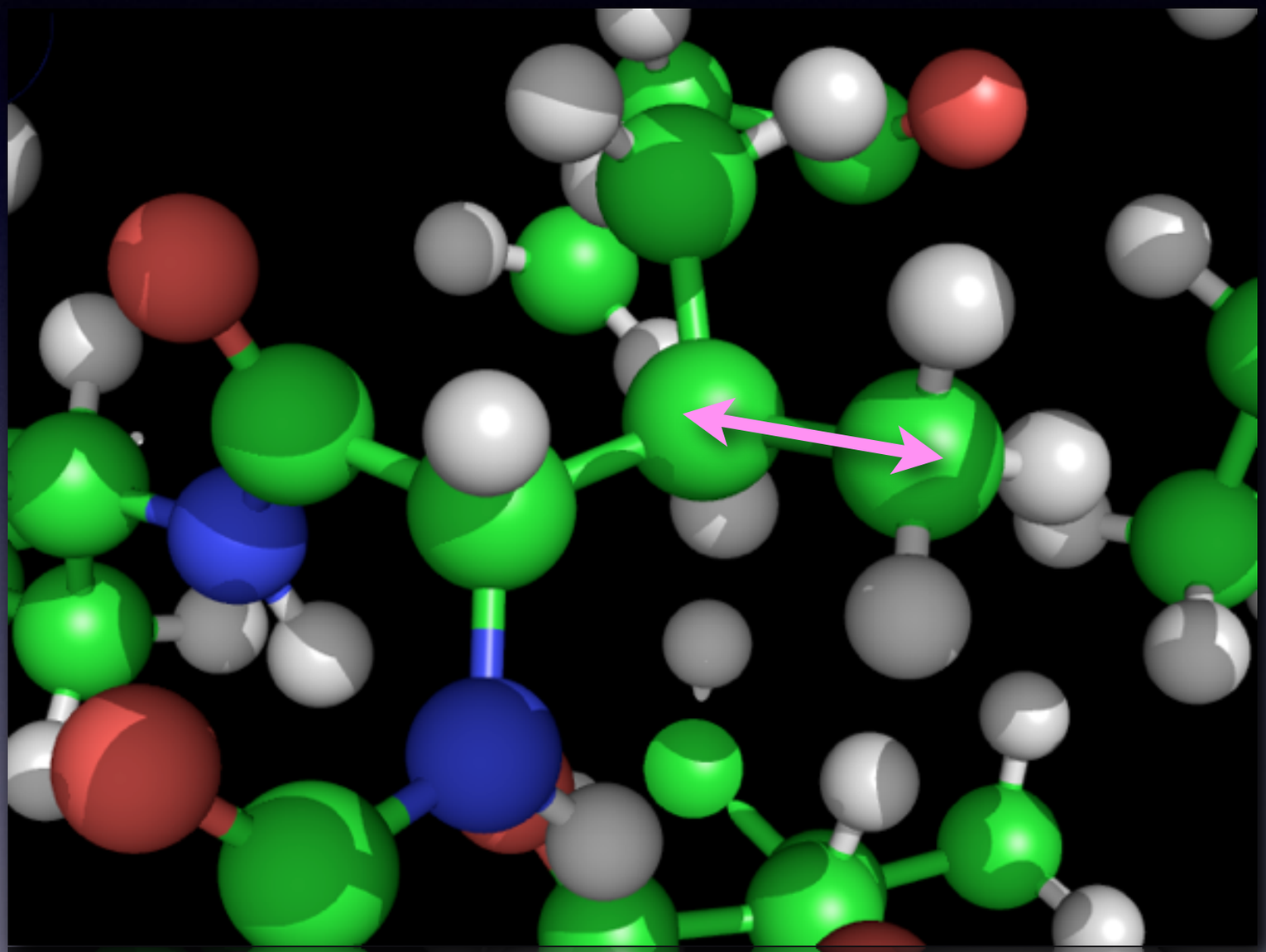




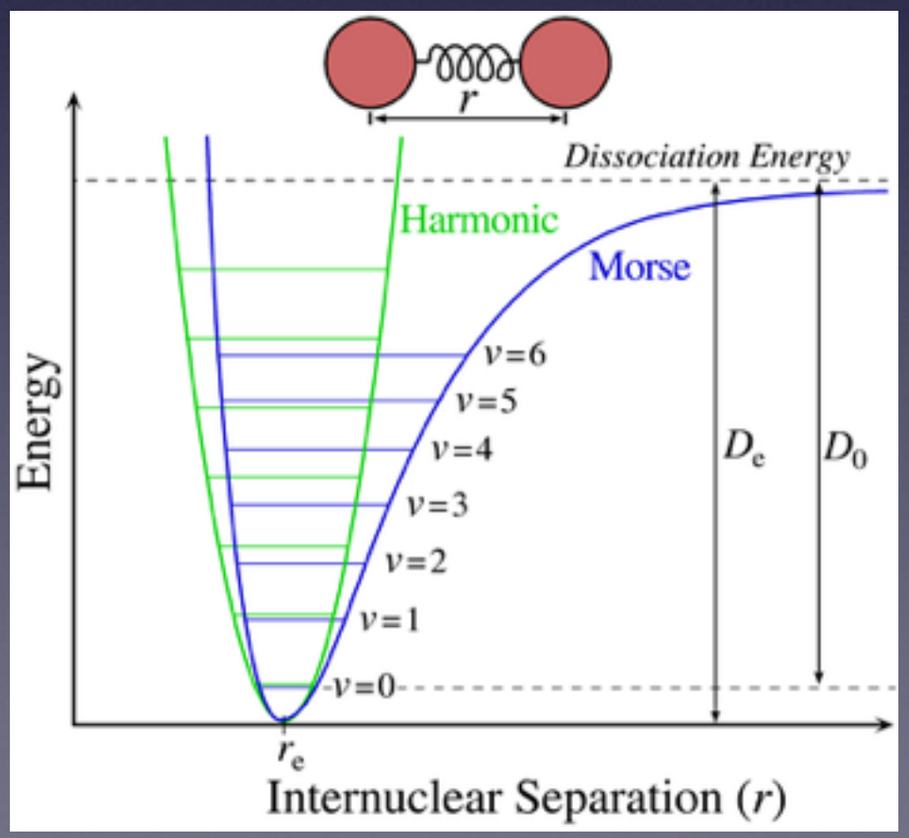
Electron clouds are mobile, with density varying between different atoms!

Bond stretching

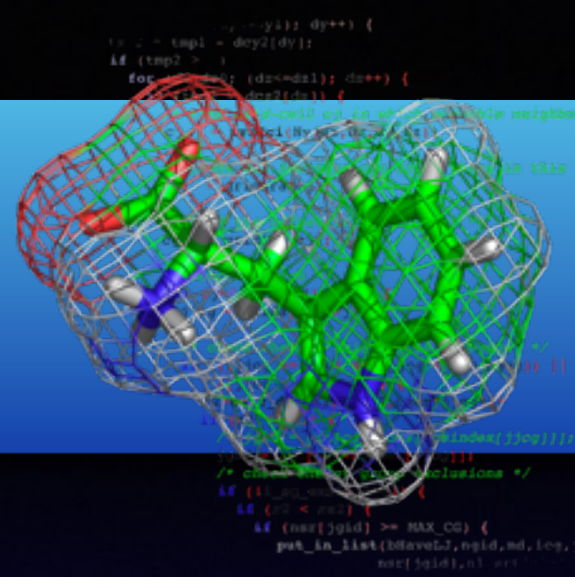


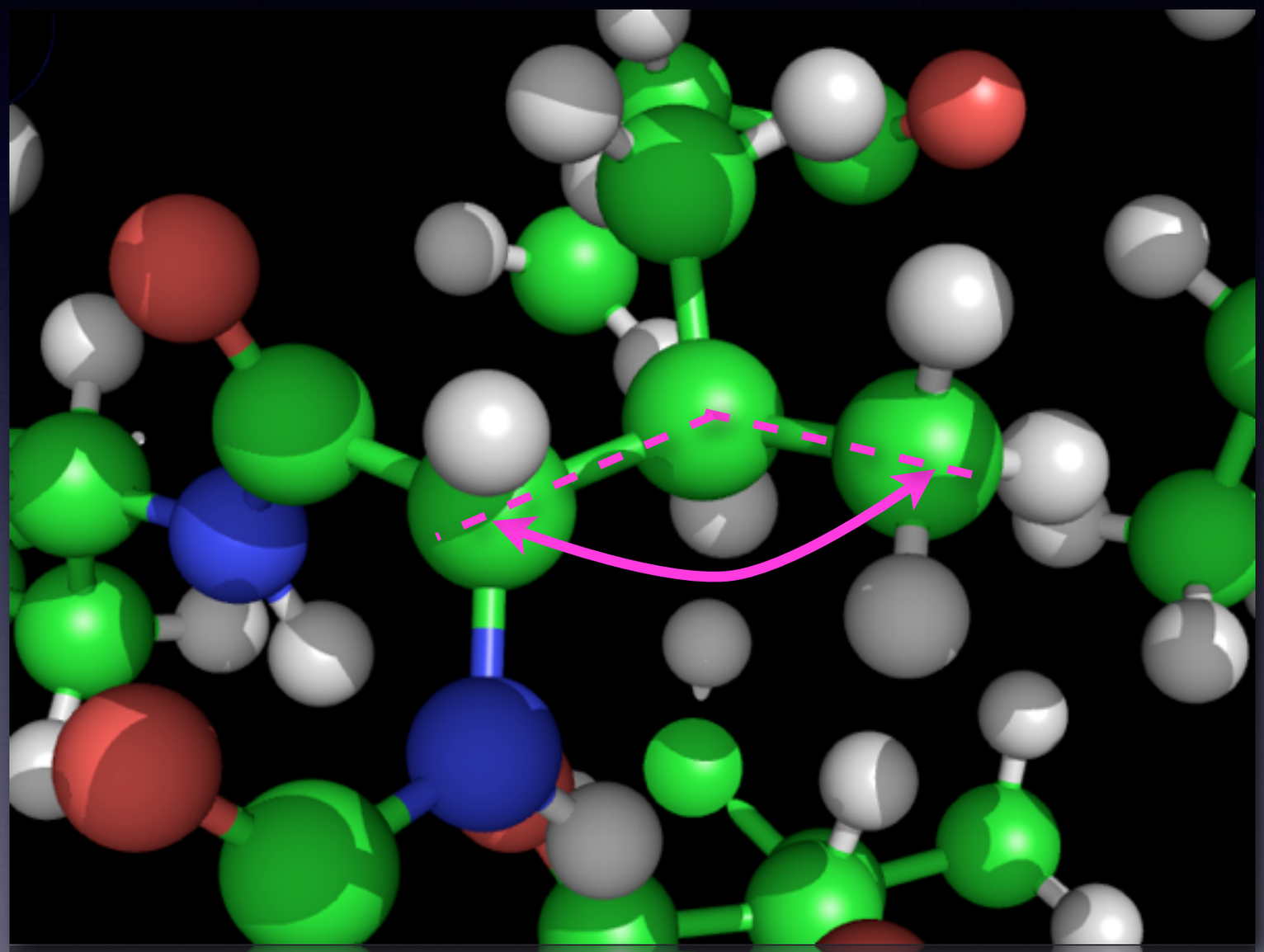


- $V = k\,\Delta x^2$
- $V = D\,(1 - e^{-ax})^2$



Angle vibrations

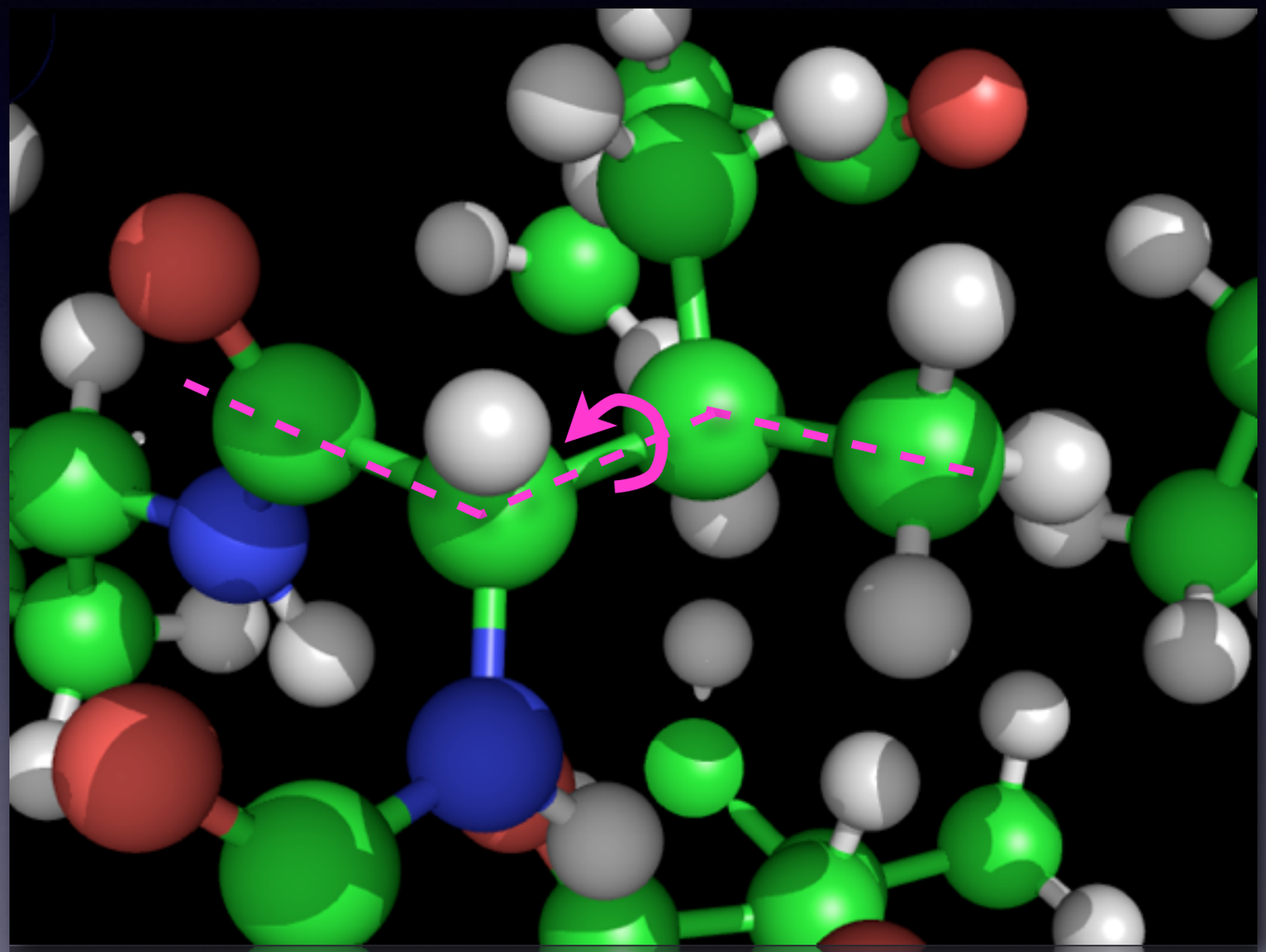




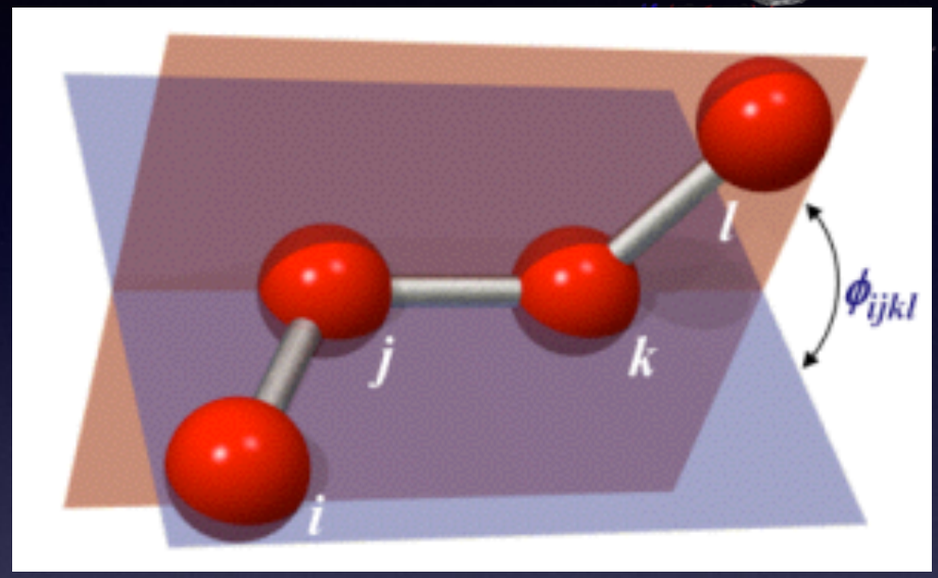
Similar to bonds:
Should really be a QM oscillator, but can be approximated well

Not quite as rigid as a bond, but almost

Torsions/dihedrals



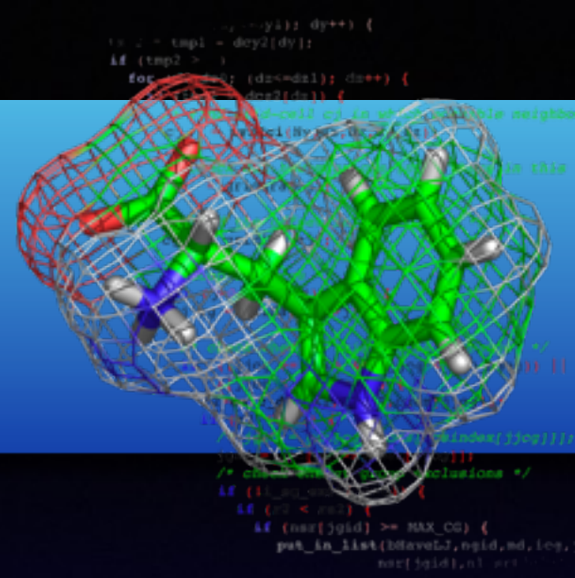
Important! Gives rise to the Ramachandran diagrams

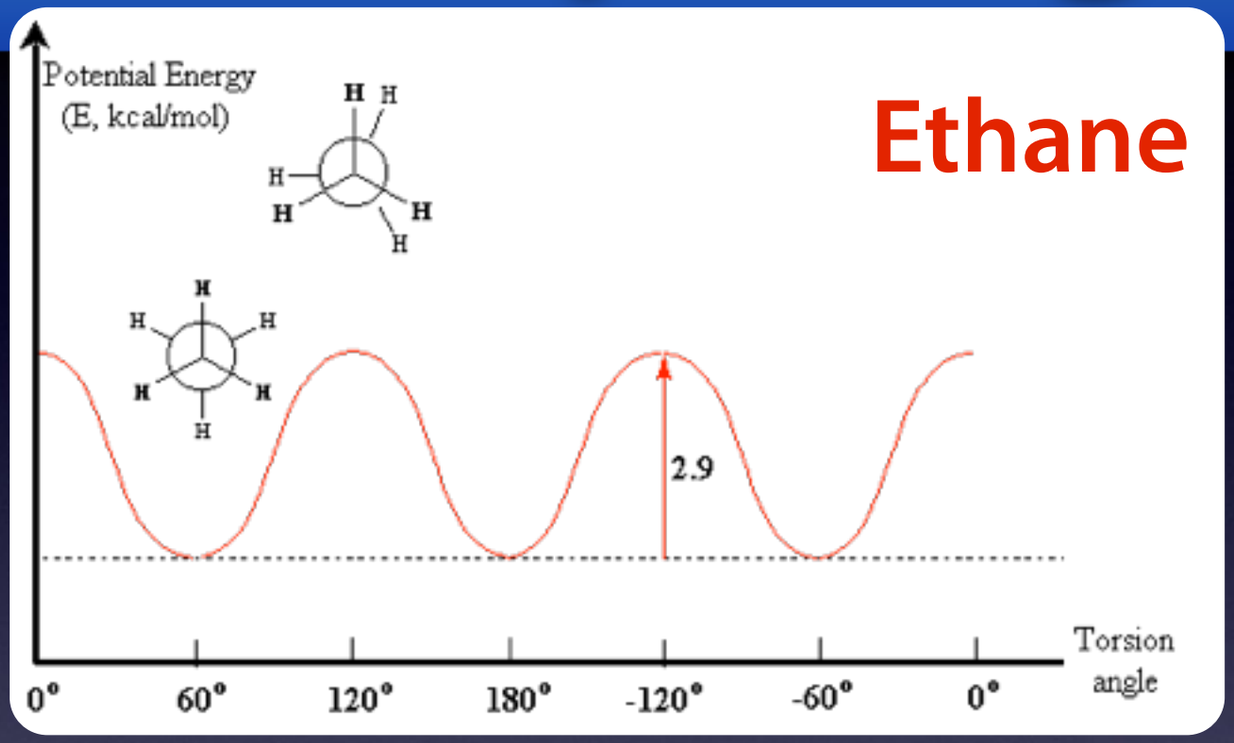


Frequently called "dihedral" angle too

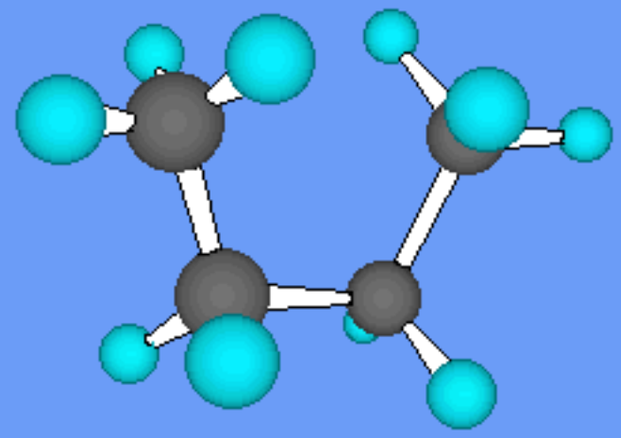
Angle between planes defined by atoms i-j-k & atoms j-k-l

Comparing torsions

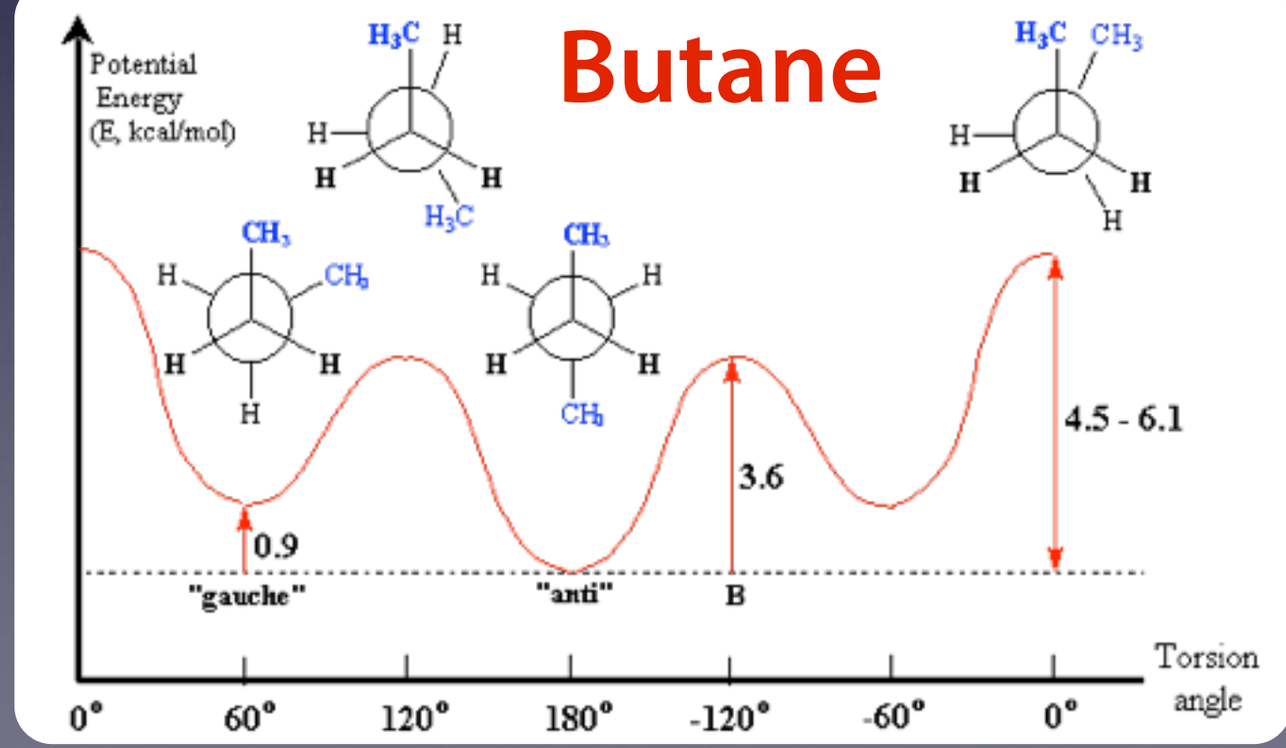




Ethane

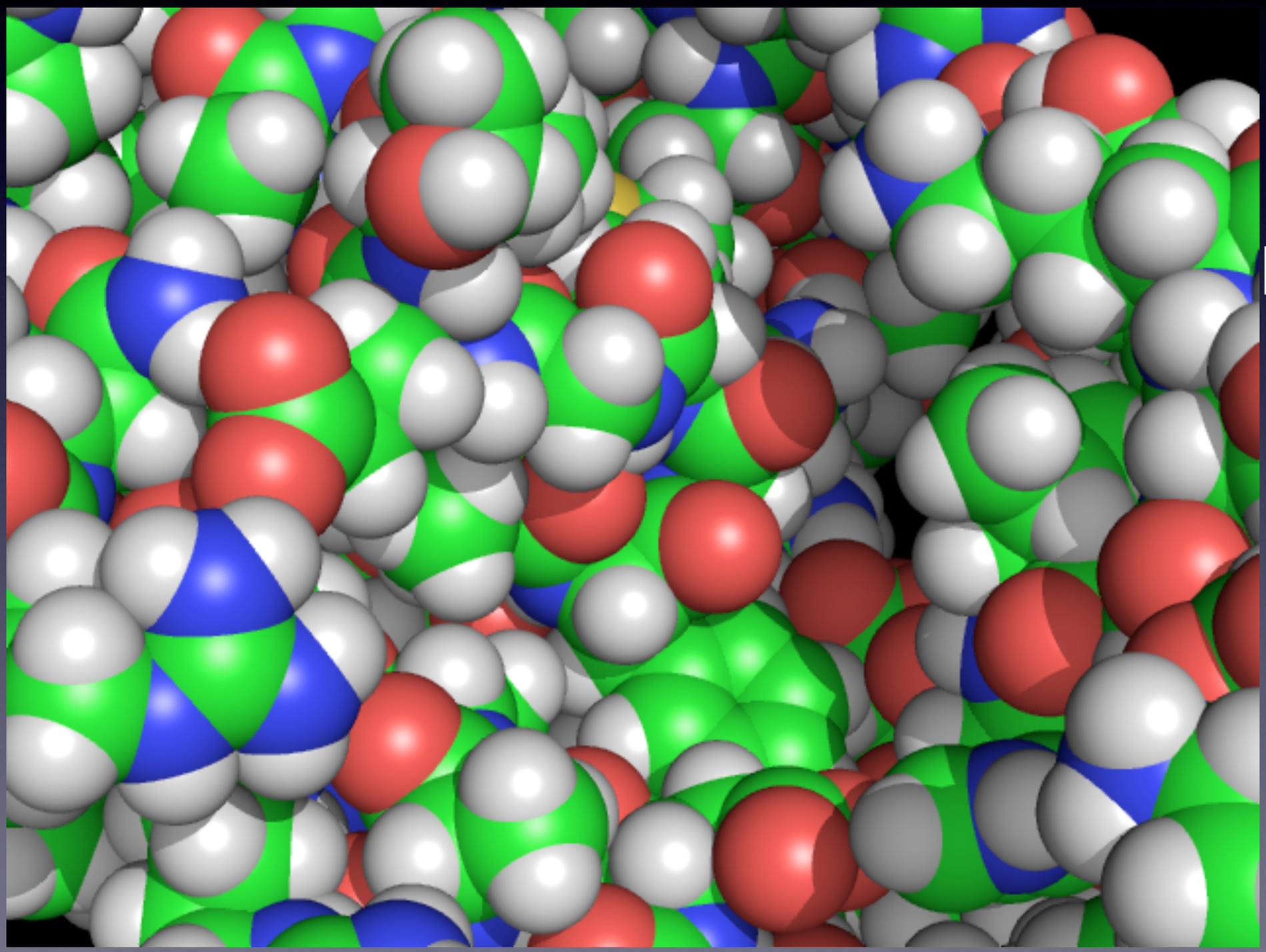


Butane



Butane

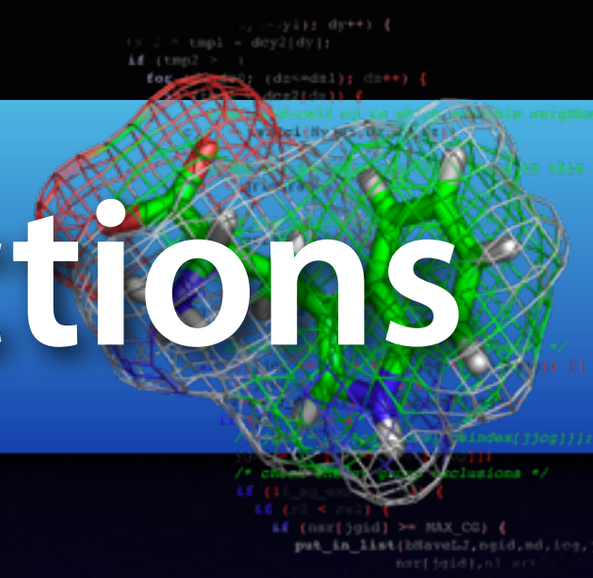
Nonbonded interactions



Packing effects

Electrostatics

van der Waals interactions



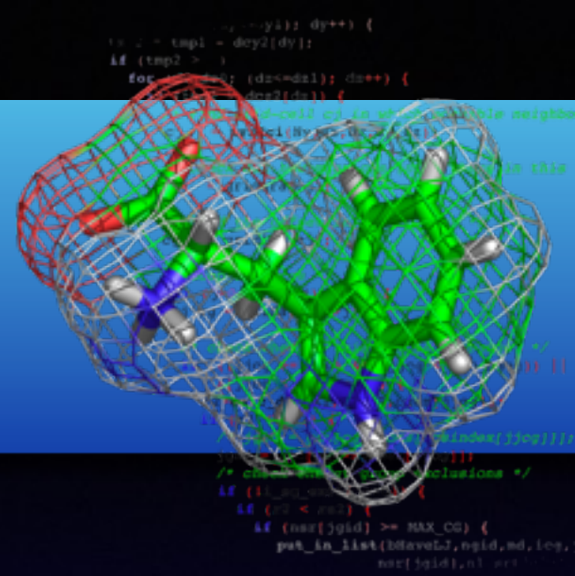
- Atoms repel each other at close distance due to overlap of electrons (repulsion)
- All atoms attract each other at long distance due to induced dipole effects (dispersion)

Example - Buckingham potential:

$$V(r) = A\exp^{-Br} + \frac{C_6}{r^6}$$

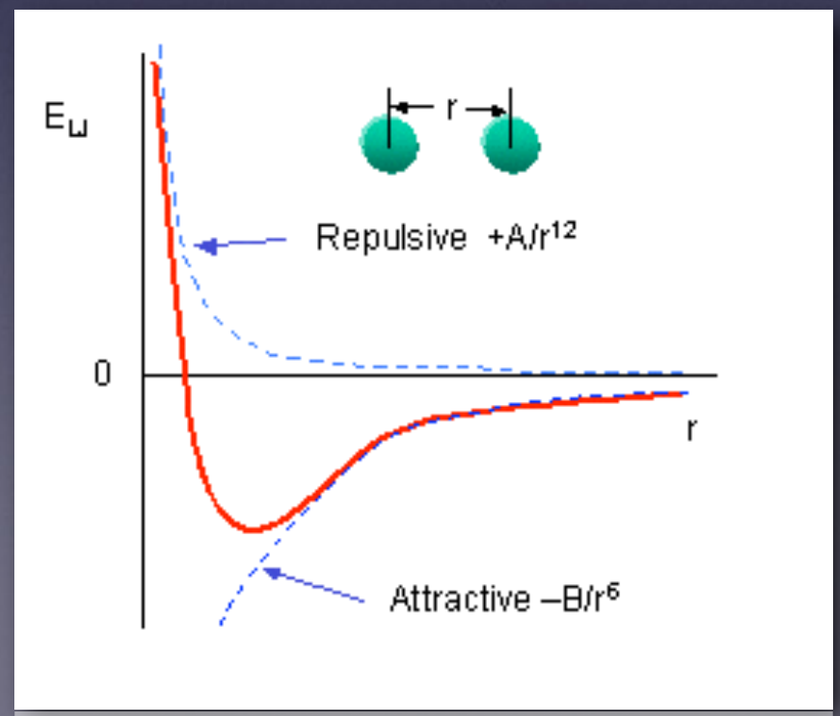
exp(r) is slow to calculate

Lennard-Jones

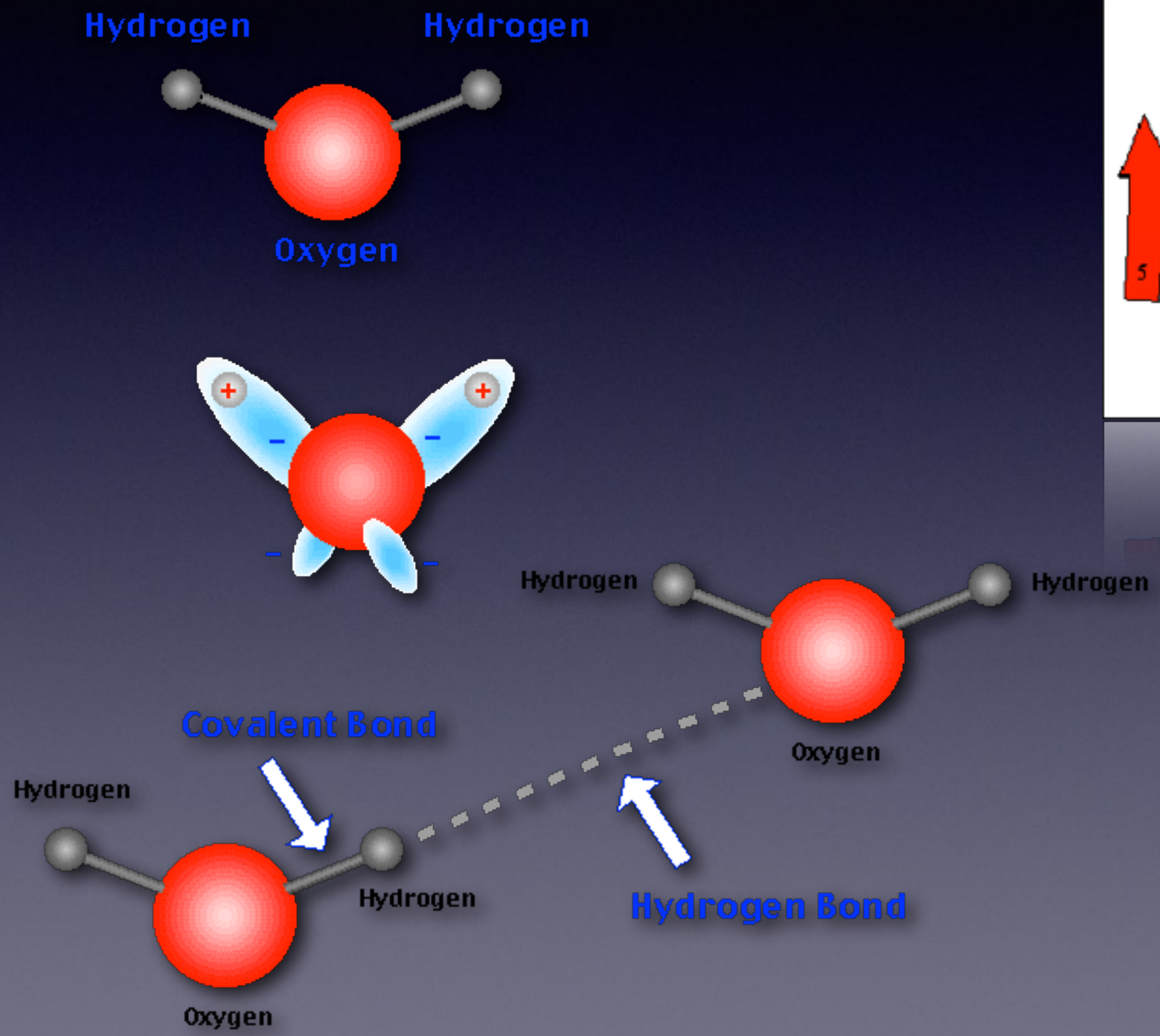


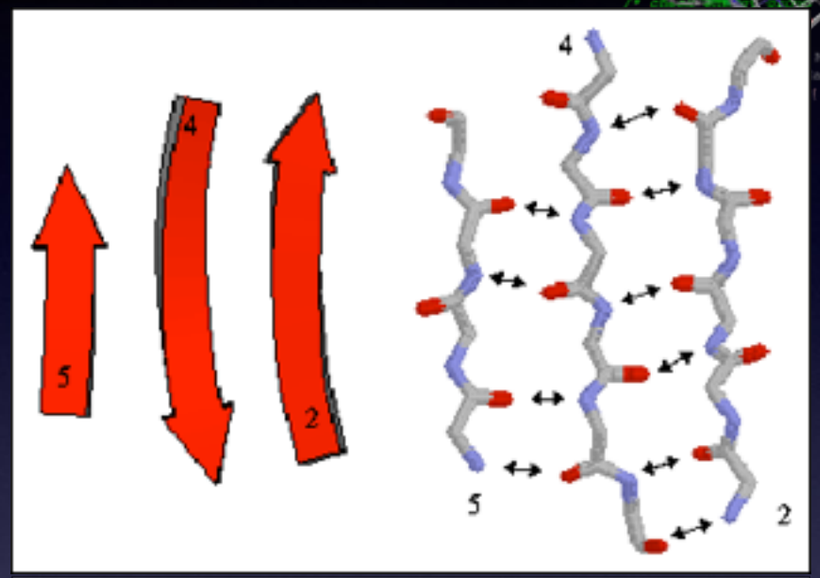
- Simpler form than Buckingham
- In practice, atoms should never approach really close, so we just want a basic model of the repulsion
- Smart trick: When we have calculated $1/r^6$, it is trivial to get $1/r^{12}$ (1 multiplication)
- Lennard-Jones potential

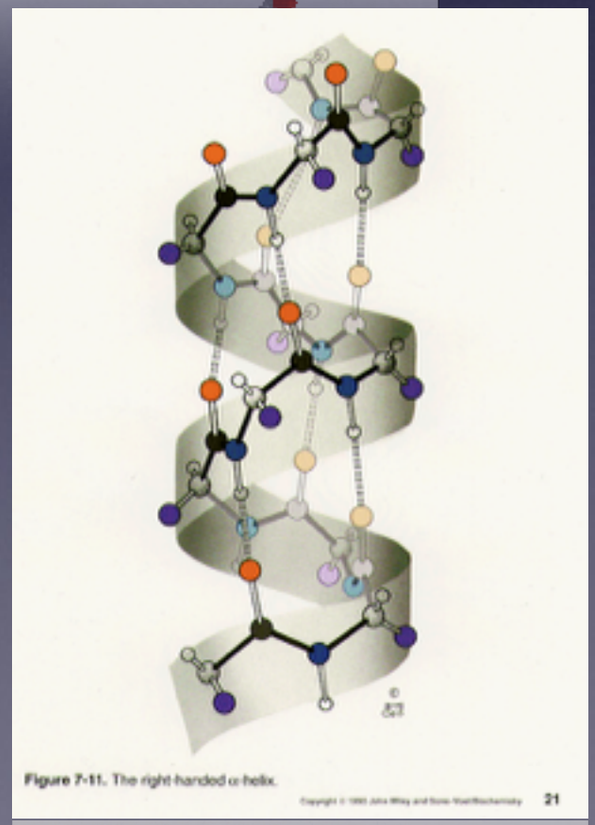
$$V(r) = \sum_{i=1}^{N} \sum_{j=1}^{N} \left(\frac{C_{12}}{r_{ij}^{12}} - \frac{C_6}{r_{ij}^{6}} \right)$$



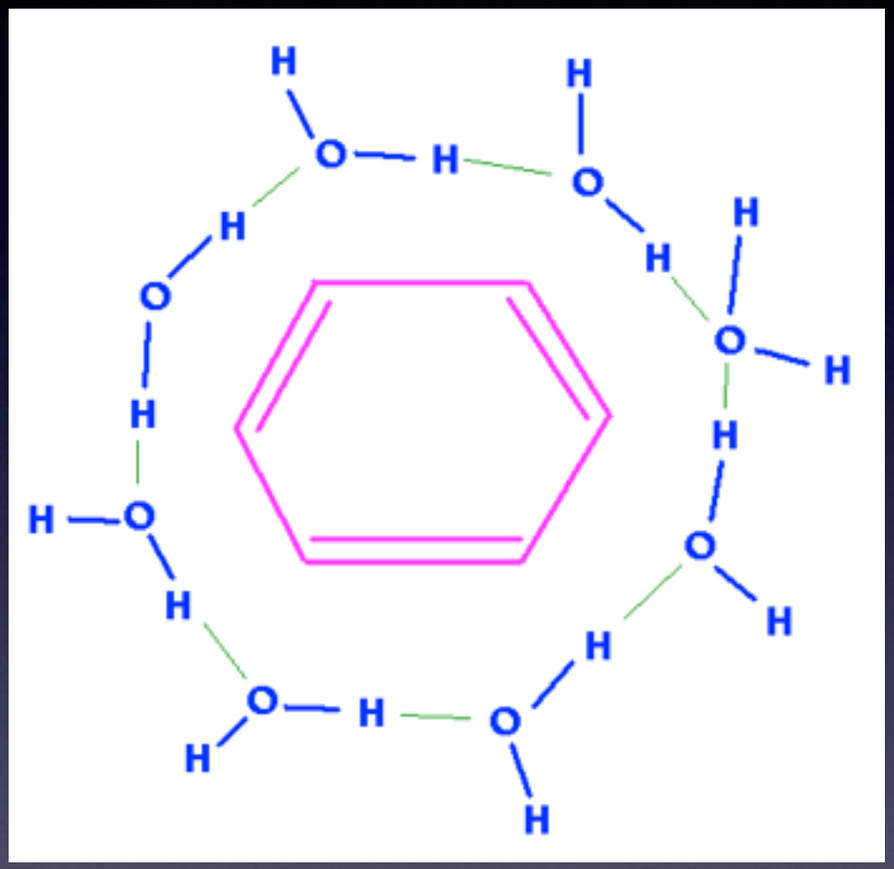
Hydrogen bonds in proteins

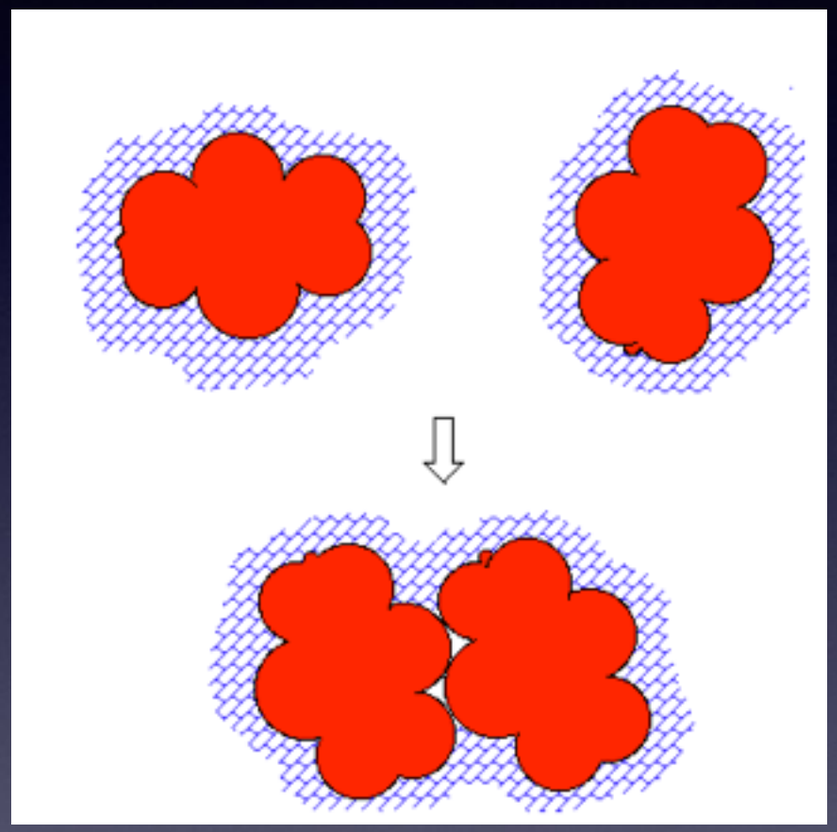


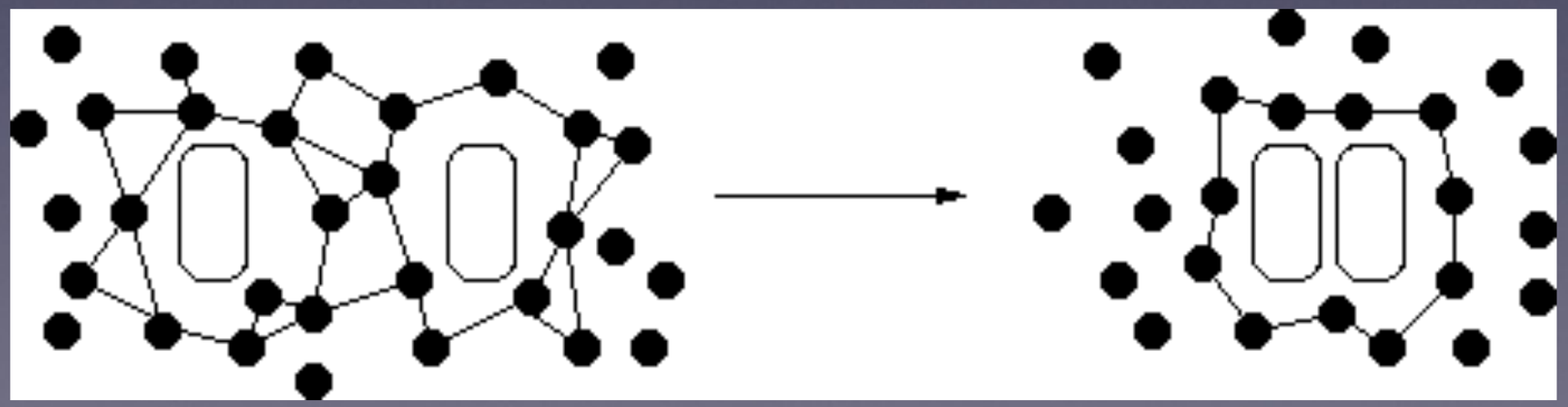




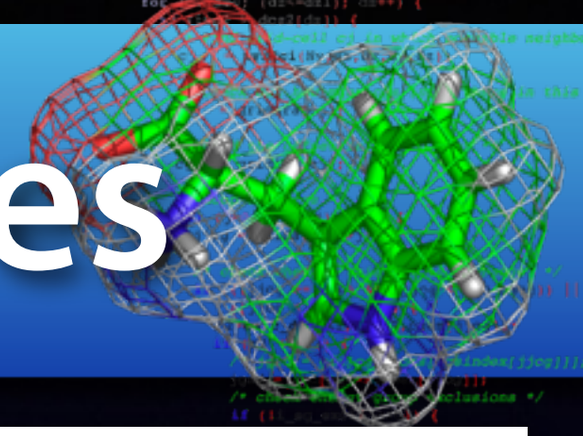
Hydrophobic effect





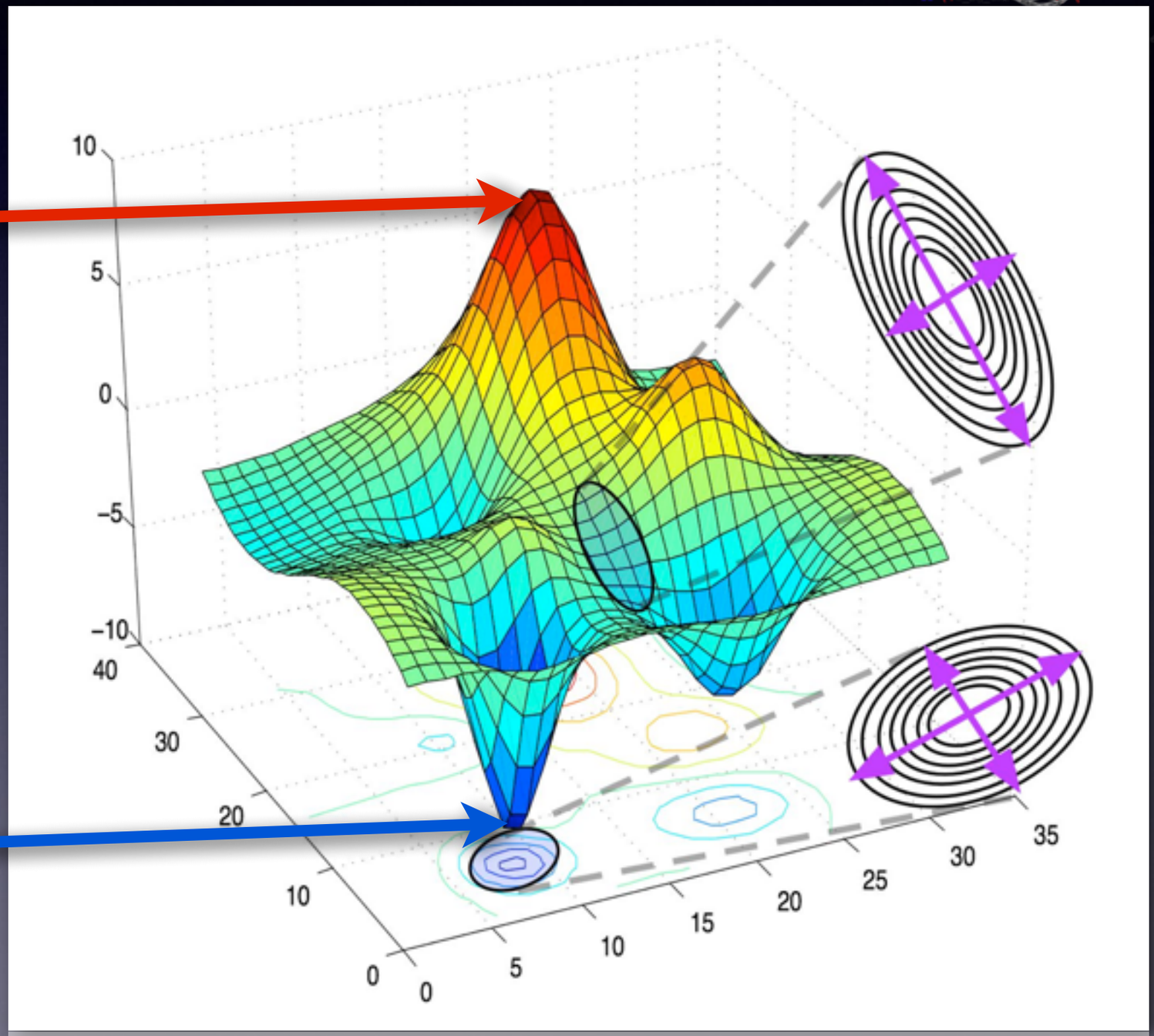


Energy Landscapes



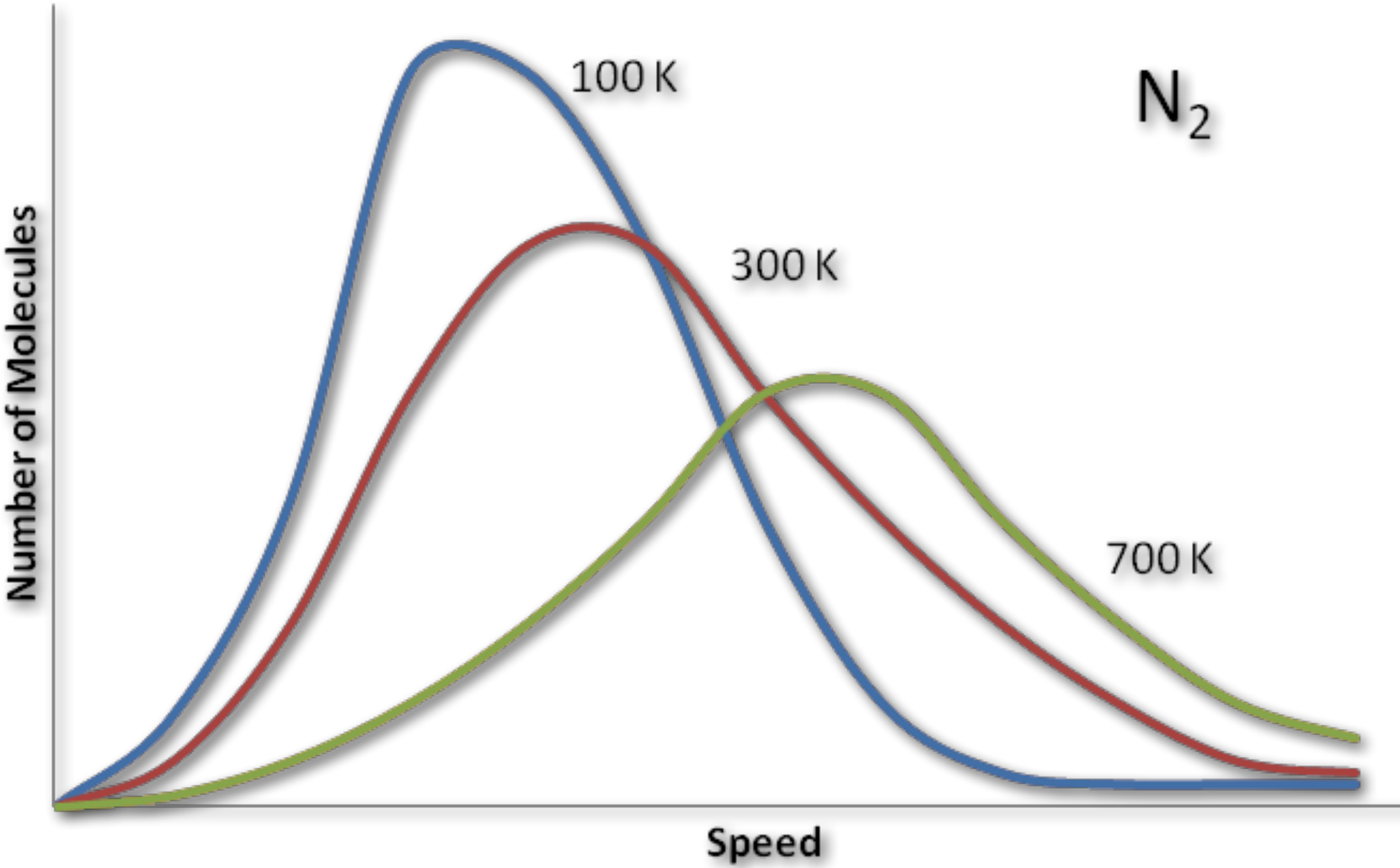
Bad?

Good?



The Boltzmann Distribution

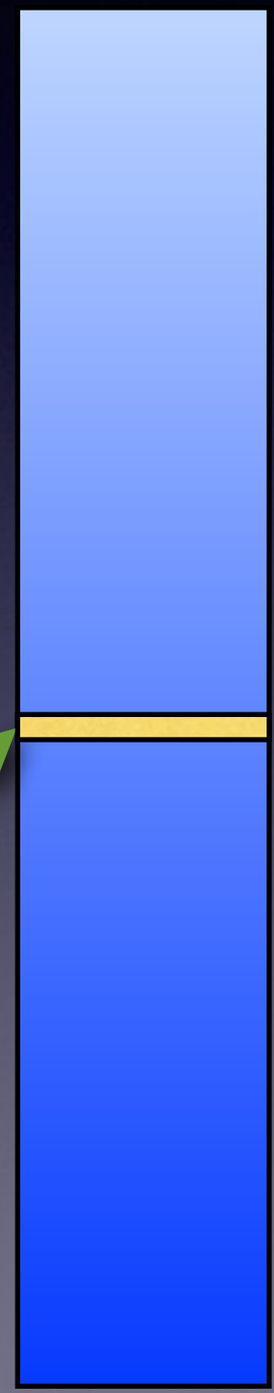
$$\rho \propto e^{-\Delta E/kT}$$


100 K
300 K
700 K
N_2
Number of Molecules
Speed

Formulating Boltzmann

- Follow the book and derive it for a special case first: ideal gas in tall cylinder

How many (N) molecules here? Function of potential energy E!



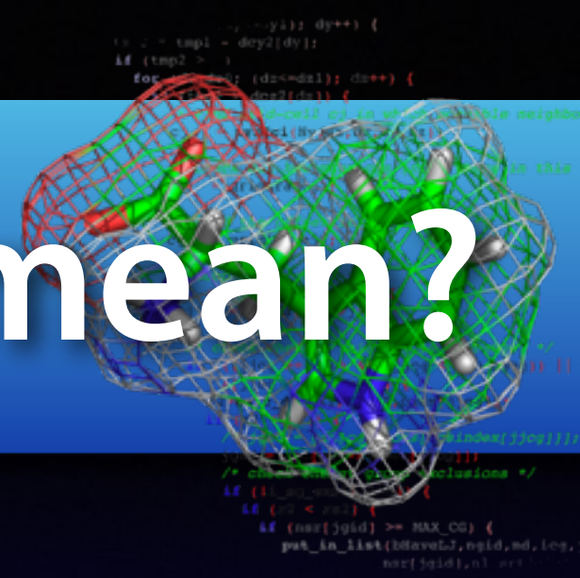
E(h)=mgh

Gravity ↓ ↑ Pressure

Formulating Boltzmann

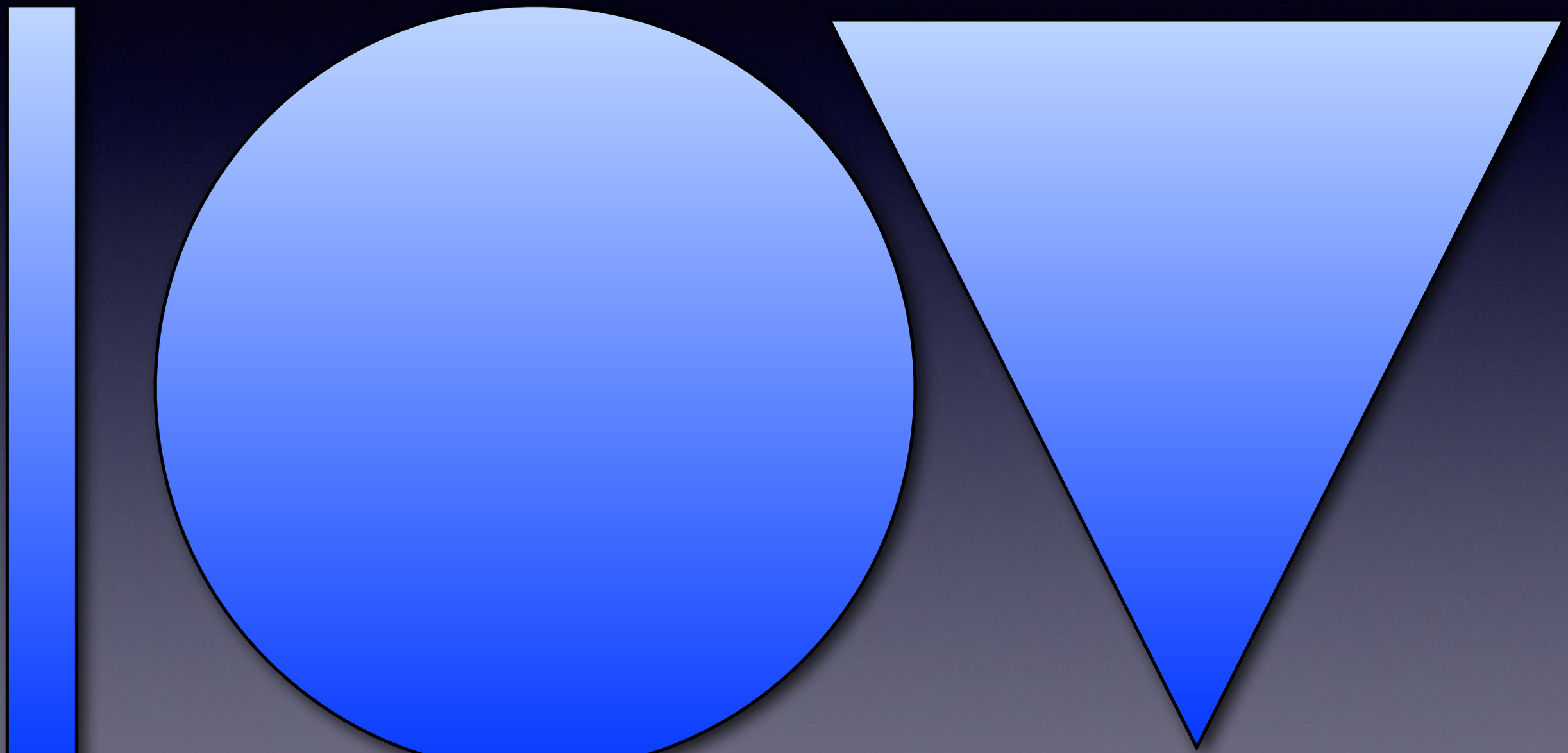
- Clapeyron's gas law: P=N k T
- Potential energy (gravity): E(h)=m g h
- dP/dh=(dN/dh)kT
- dP=(m g N)(-dh)
- dP/dh=(dN/dh)kT=-m g N
- dN/dh=-(mg/kT) N
  - And use: (dN/dh) / N = d[ln(N)]/dh
- d[ln(N)]/dh=-mg/kT
  - Integrate & take exponential of both sides
- $N \propto \exp\{-m\,g\,h/kT\} = \exp\{-E(h)/kT\}$

What does Boltzmann mean?



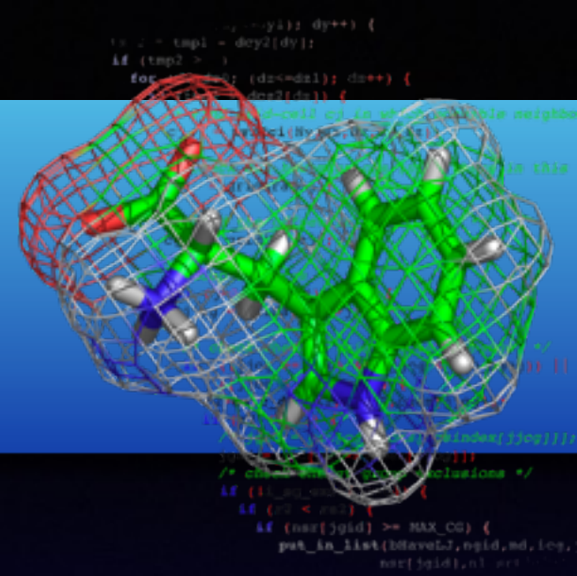
- Probability of being at energy E_A:
  $pE_A \propto \exp\{-E_A/kT\}$
- Compare with energy E_B:
  $pE_A/pE_B = \exp\{-E_A/kT\} / \exp\{-E_B/kT\}$
- Lower-energy states will be more populated
- But is that everything?

Which shape is best energy-wise?



Volume matters!

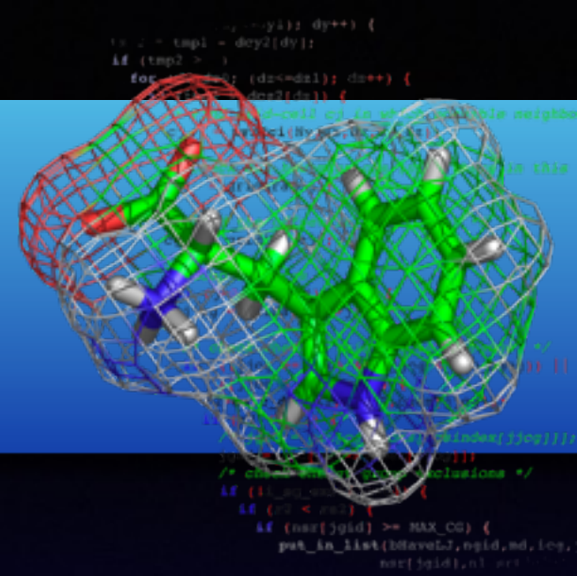
Free Energy



- Introduce the available volume V_A
- Number of states proportional to volume
- Thus, probability is proportional to volume
- Consider probabilities of finding particles somewhere in volumes A vs. B:

$$pV_A/pV_B = (V_A \exp\{-E_A/kT\}) / (V_B \exp\{-E_B/kT\})$$

Free Energy



- Use V=exp{ln(V)}
- This gives us:

$$pV_A/pV_B = \exp\{-E_A/kT+\ln V_A\} / \exp\{-E_B/kT+\ln V_B\} = \exp\{-(E_A-T*k \ln V_A)/kT\}/\exp\{-(E_B-T*k \ln V_B)/kT\}$$

- Looks just like a Boltzmann distribution?
  But now it says (E-T*k ln V) instead of E?

Entropy & Free Energy

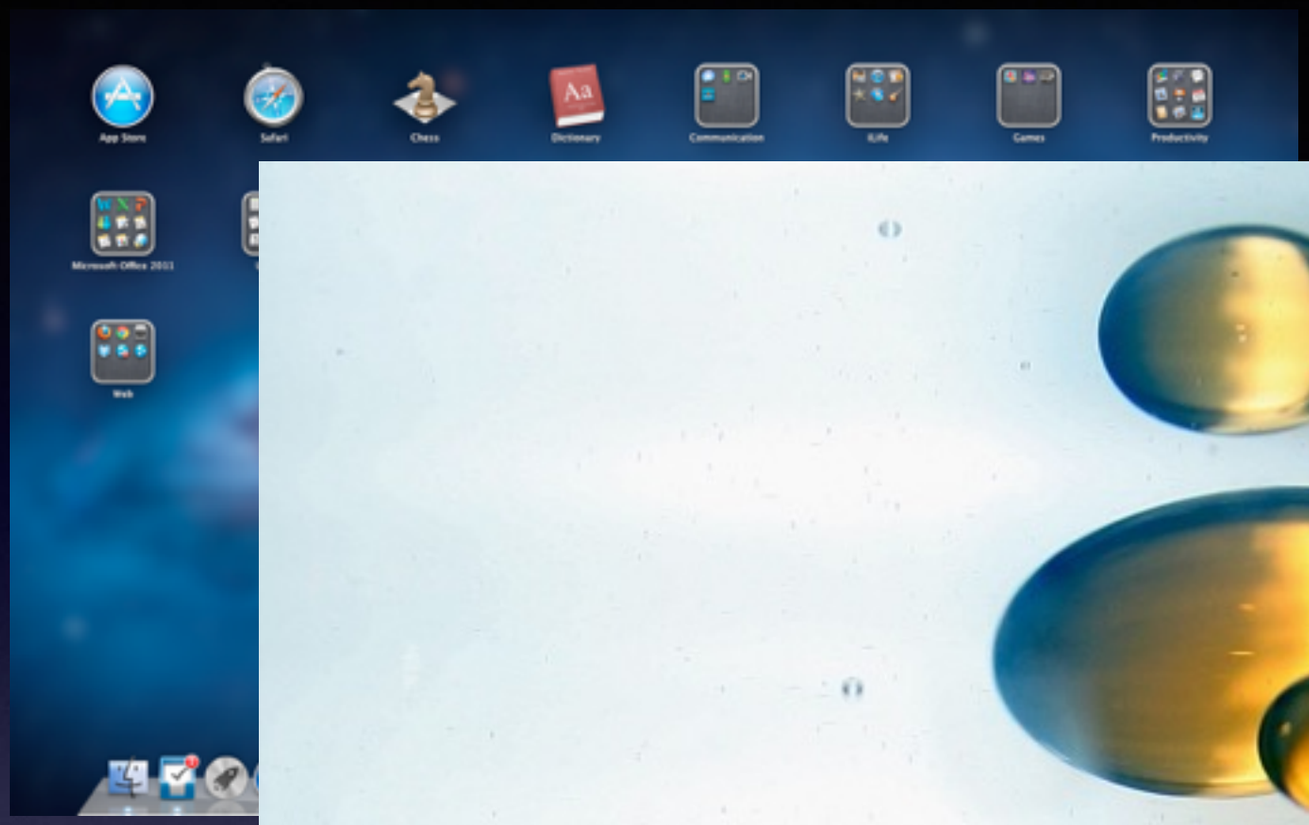
- Introduce *Free Energy*: F=E-T*k ln V
- Entropy: S=k ln V (logarithm of #states)
- F = E - TS
- $p_A/p_B=\exp\{-F_A/kT\}/\exp\{-F_B/kT\}$
- $p_A/p_B=\exp\{-\Delta F/kT\}$

How many states does this correspond to? *1!*

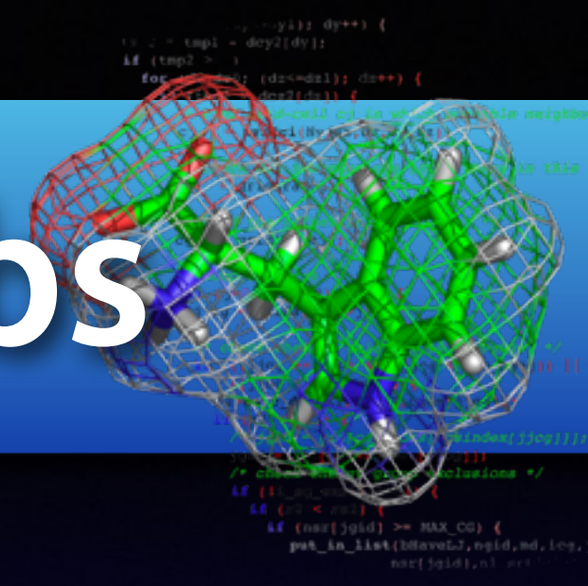
How many similar states are there? *few*

How many states does this correspond to? *1!*

How many similar states are there? *lots*

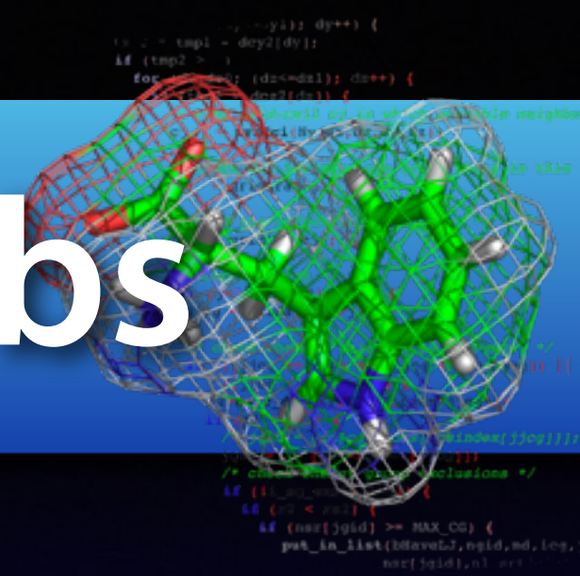

App Store
Safari
Chess
Dictionary
Communication
iLife
Games
Productivity
Microsoft Office 2011
Web

Helmholtz & Gibbs

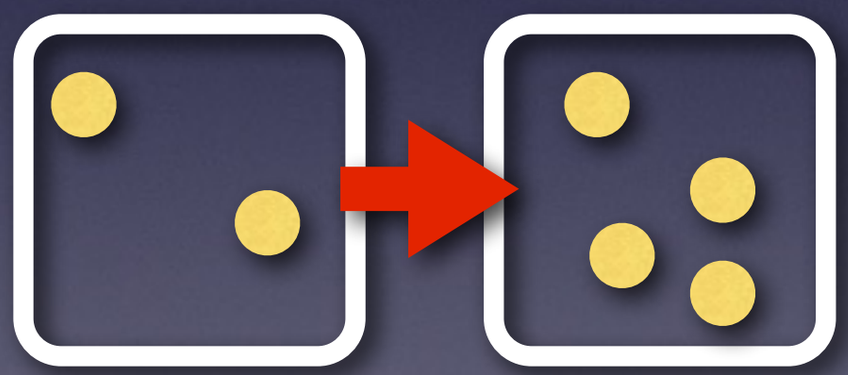


- Free energy defines most stable state when system *exchanges heat* with surrounding environment
  - F is the Helmholtz Free Energy
    - Valid at constant volume
  - Gibbs Free Energy G=H-TS=E+pV-TS

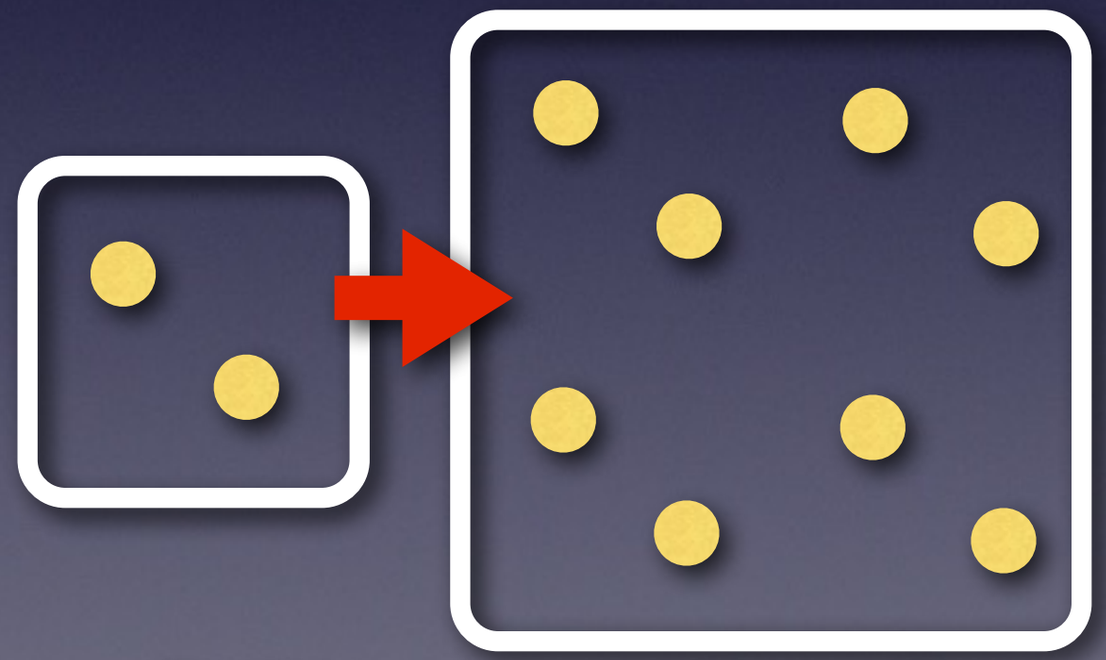
Helmholtz vs. Gibbs



- F = E-TS
- G = E+pV-TS = H - TS



F, E not proportional to # particles

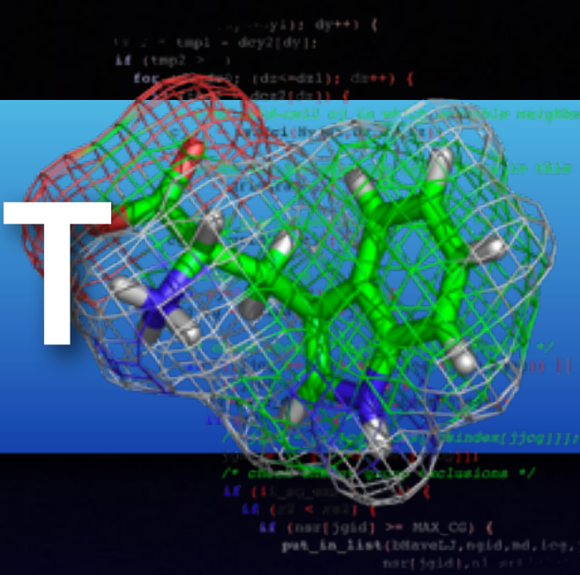


G, H proportional to # particles

Phase Transitions Explained

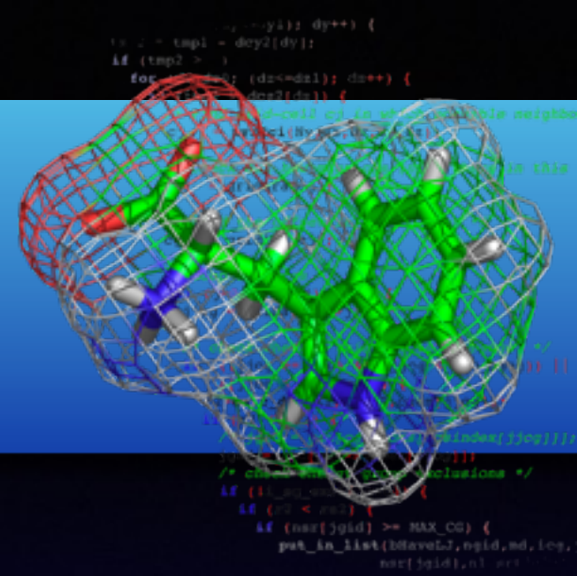
- Systems wants to stay at lowest F
- ICE: Low E, low low S
- Water: Higher E, higher S
- When temperature is low, first term (E) dominates F=E-TS
- When temperature is high, second term (TS) dominates F=E-TS

Thermodynamic T



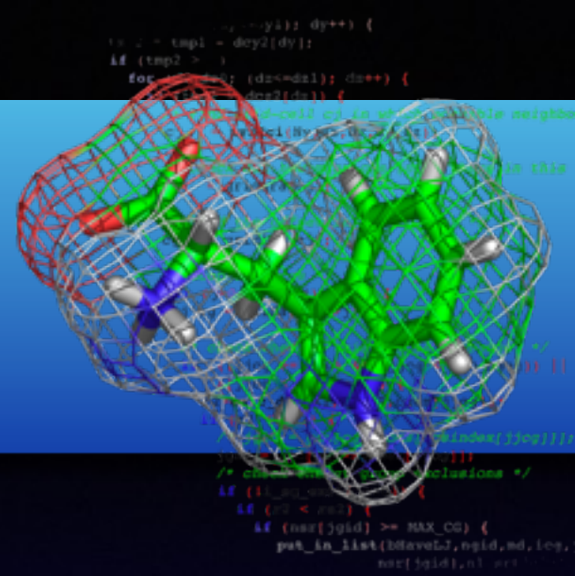
- Minor perturbations:
- F->F+dF = F + dE - TdS - SdT
- At equilibrium under constant V & T, this leads to:
  dF=dE-TdS=0
- or: T = dE/dS
- This is the thermodynamic definition of temperature!

Partitioning



- Consider transfer of hydrocarbon to H_2O
- Concentrations (X) iso. probabilities
- Count per mol, so R instead of k
- $X \propto \exp\{-G/RT\}$
- $\Delta G_{liq->aq} = -RT \ln (X_{aq}/X_{liq})$
- Free energies can be measured in lab!

Reality Check



- Chapters 3 & 4 in “Protein physics”
- Amino acids determine protein structure
- Electrostatics & hydrogen bonds
- Van der Waals / Lennard-Jones
- Interactions that determines:
  - Free energy via
  - the Boltzmann Distribution