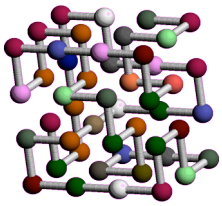
# Protein Folding 2

Thermodynamics
Lattice Model
Design of foldable proteins
Calculations of Z-score

## Lattice Model



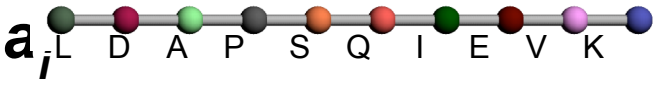
- Amino acids sit in the nodes of the cubic lattice.
- They interact with their neighbors on the lattice.
- It's very hard to fold such protein: LEVINTHAL PARADOX

# Energy function

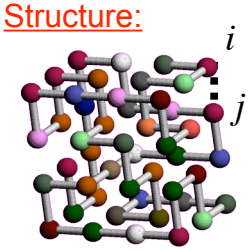
Energy function:

$$E = \sum_{i+1<j} \Delta_{ij} U(a_i, a_j)$$

Sequence:



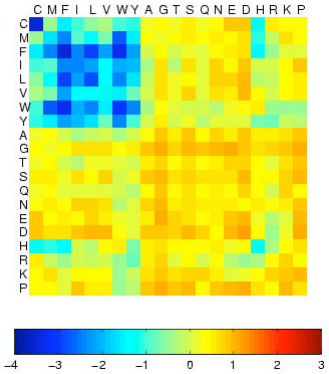

Structure:




$\Delta_{ij} = 1$ if *i* and *j* are in contact

$\Delta_{ij} = 0$ otherwise

Potential: ***U(x,y)***

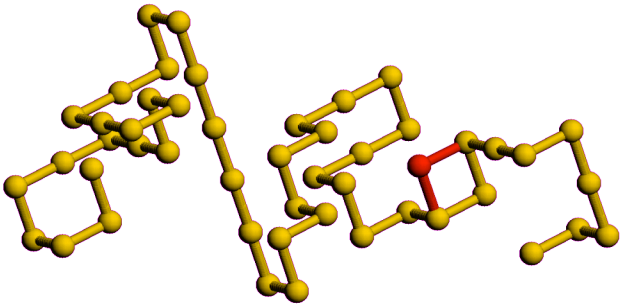



# Monte Carlo Dynamics

1. Pick a fragment.
2. Try a move
3. Compute ΔE
4. Accept the move with probability P

P=1 if $\Delta E \le 0$

P=exp(-ΔE/T) if $\Delta E > 0$



•What do you expect to see at low T?
high T?

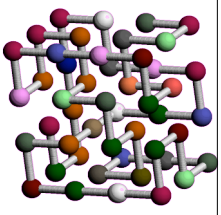
# Demo

# Evolving a foldable sequence = sequence with a large energy gap

Three approaches to obtain foldable sequences:

1. Maximize $\frac{E_n - \langle E \rangle}{E_c - \langle E \rangle}$
2. Minimize $Z = \frac{E_n - \langle E \rangle}{\sigma(E)}$
3. Minimize $E_n$, *while constraining amino acid composition (i.e. $\sigma$ and <E>)*

$$\boxed{E = E(\vec{a}, \Delta, U); \quad E_n = E(\vec{a}, \Delta_n, U);}$$



Algorithm: Metropolis Monte Carlo (for case 3: minimize the energy in the native structure)

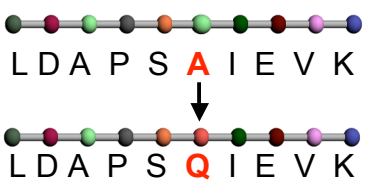
1. Pick the Native Structure, a starting (random) sequence, and a potential U(x,y)
2. Mutate the sequence and calculate the change in $E_n$ : $\Delta E_n = E_n(a') - E_n(a)$
3. Accept or reject the mutation: accept with Prob=max{1,exp(-$\Delta E_n$/Tseq)}
4. Go to step 2.

This satisfies Detailed Balance:

$$\frac{P(\vec{a} \to \vec{a}')}{P(\vec{a}' \to \vec{a})} = \exp\left[ -\frac{E(\vec{a}') - E(\vec{a})}{T_{seq}} \right]$$

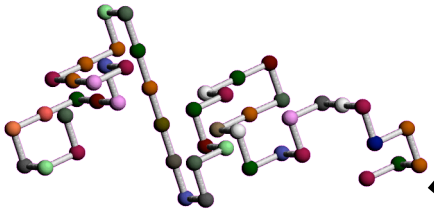
Conversing to equilibrium

$$P(\vec{a}) = \exp\left[ -\frac{E(\vec{a})}{T_{seq}} \right]$$

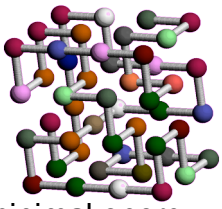


# Evolved proteins can fold!

Random conformation



Folding Time:
$\langle t \rangle = 10^6\text{-}10^8$ for 48-mer
$\langle t \rangle = 10^5\text{-}10^7$ for 27-mer



Conformation of minimal energy

Folding time depends on the sequence and structure of the protein!