PROTEIN FOLDING 10/14/19

→ FOLDING IS COOPERATIVE AND OFTEN TWO-STATE.

→ PROTEINS ARE MARGINALLY STABLE, WITH STABILITIES FROM 5-100 kJ/mol

→ DRIVING FORCE COMES FROM HYDROPHOBIC EFFECT*

→ STRUCTURE COMES FROM HUGE PENALTIES FOR PULLING HYDROGEN BONDS FROM WATER INTO UNFULFILLED STATES

HOW DO PROTEINS EVEN FIND NATIVE STRUCTURE OUT OF HUGE # OF POSSIBILITIES?

→ FOLDING IS MODULAR AND HEIRARCHICAL

→ PROTEINS FOLLOW (RELATIVELY) WELL-DEFINED FOLDING PATHWAYS

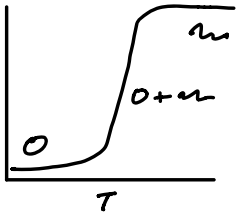
COOPERATIVE:

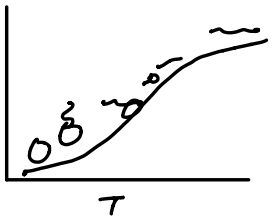
TO A GOOD APPROXIMATION, PROTEINS ARE EITHER FOLDED OR UNFOLDED.

HOW DO WE KNOW?

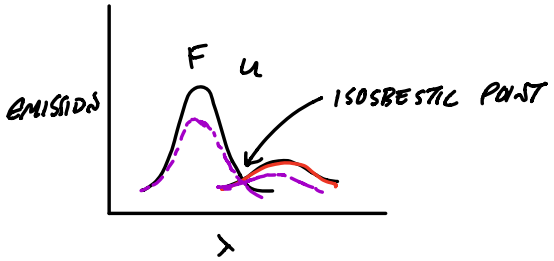
1. UNFOLDING TRANSITION IS SIGMOIDAL
2. $\frac{k_f}{k_u} = \Delta G_{FOLD}$

S





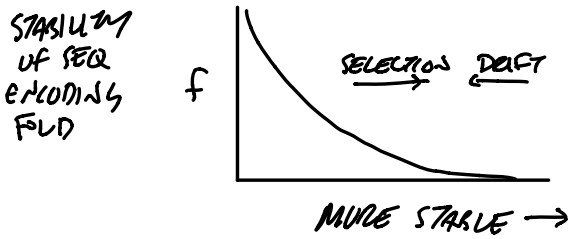
3. SPECTROSCOPY → LINEAR MIXTURE OF TWO STATES



MARGINAL STABILITY:

- BALANCE BETWEEN LARGE # OF TERMS FAVORING FOLDING, LARGE # DISFAVORING FOLDING
- SUMS TO ~Ø kJ/mol.

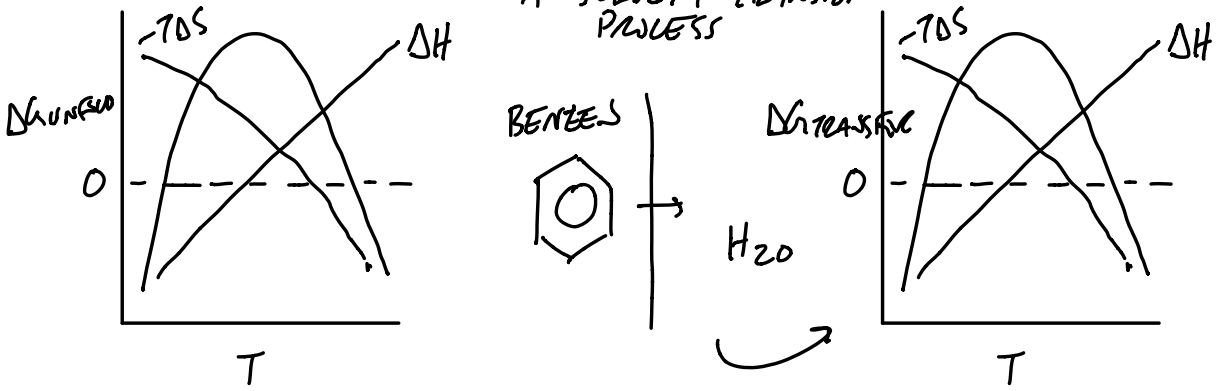
WHY?
- FUNCTION (E.G. DYNAMICS)
- REGULATION (PROTEOLYTIC TURNOVER)
- EVOLUTION (MUTATION-SELECTION BALANCE)



WAY MORE WAYS TO BE UNSTABLE THAN STABLE

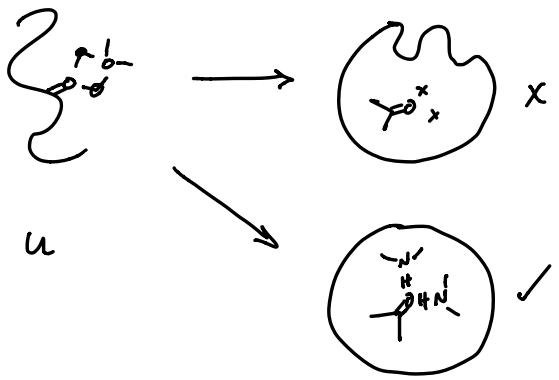
HYDROPHOBIC EFFECT

PROTEIN FOLDING WORKS LIKE A SOLVENT TRANSFER PROCESS



CAN BE QUANTIFIED USING SOLVENT ACCESSIBLE SURFACE AREAS. (WILL DISCUSS IN ~A WEEK)

STRUCTURE ARISES TO SATISFY ALL NON-COVALENT BONDS



IT COSTS ~20 kJ/mol TO ENTIRELY LOSE AN H-BOND WITH WATER.

IF YOU GO THROUGH MANY PROTEIN STRUCTURES AND CAREFULLY COUNT UNFULFILLED H-BONDS, ONLY ~1:5,000 HAVE NO PARTNER. "STATISTICAL POTENTIAL" IS

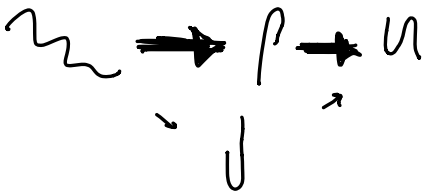
$-RT\ln(5000/1) = -21\ kJ/mol$

HOW DO PROTEINS FIND THEIR FOLDED STATE OUT OF ALL POSSIBILITIES?

FOLDING IS MODULAR AND HIERARCHICAL

- SECONDARY STRUCTURE → DOMAINS → ASSEMBLIES
- BIAS TO STRUCTURE: BITS OF IT FORM TRANSIENTLY EVEN IN THE UNFOLDED STATE. MOST STRUCTURES ARE NOT POSSIBLE.

MOSTLY WELL-DEFINED FOLDING PATHWAYS.

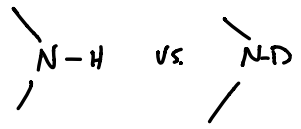


EVIDENCE:

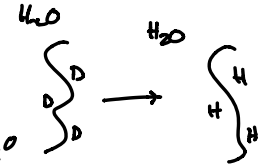
SIMULATIONS → SAME PATH SEEN AGAIN AND AGAIN

HDX MASS SPEC

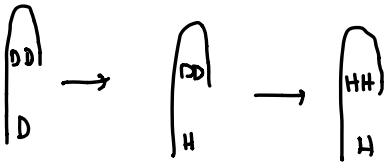
DIFFERENT MASSES



EXCHANGE



CAN MAP FOLDING PATHWAYS



COOL BIT: CAN SEE NON-LOCAL FOLDING EARLY.