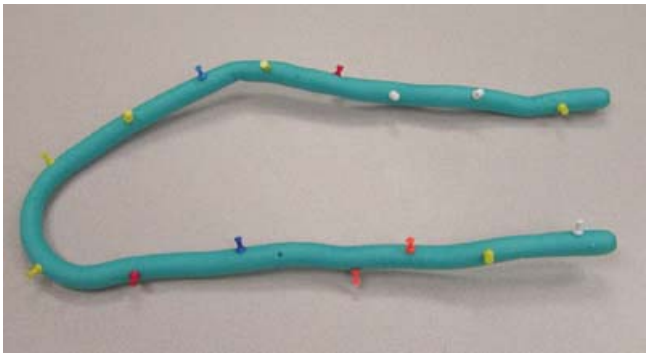
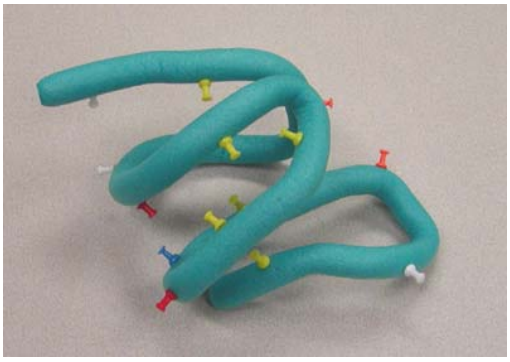
Center for BioMolecular Modeling
...where teachers come first

Protein Folding with 15 Tacks and a 4 Foot Toober





Explore the forces that drive protein folding with 15 tacks and a 4 foot toober. The color-coded tacks represent the sidechains of the following amino acids:

Blue Tacks	**(2)**	**basic amino acids (+ charge)**
Red Tacks	**(2)**	**acidic amino acids (- charge)**
Yellow Tacks	**(6)**	**hydrophobic amino acids**
White Tacks	**(3)**	**polar amino acid**
Green Tacks	**(2)**	**cysteine amino acid**
	15 tacks	

Instructions

1. Distribute the 15 tacks randomly but evenly along the toober. By doing this, the "tacked toober" represents a protein made of 15 amino acids.

2. Fold your protein, following the laws of chemistry that drive protein folding. (These laws of chemistry are reviewed on page 2 of these instructions.)

Basic Laws of Chemistry that Drive Protein Folding

Stably folded proteins simultaneously satisfy several basic laws of chemistry including:

1. ***Hydrophobic sidechains*** (yellow tacks) will be buried on the inside of the globular protein, where they are hidden from polar water molecules.

2. ***Charged sidechains*** (blue and red tacks) will be on the surface of proteins where they often neutralize each other and form salt bridges.

3. ***Polar sidechains*** (white tacks) will be on the surface of the protein where they can hydrogen bond with water.

4. ***Cysteine sidechains*** (green tacks) often interact with each other to form covalent disulfide bonds that stabilize protein structure.

Teaching Tips

Students should have no trouble folding their toober so that all of the yellow, hydrophobic tacks are clustered together in the central core of the folded structure. However, it may be difficult to maintain this structure while **simultaneously:**

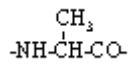
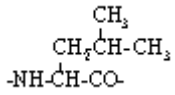
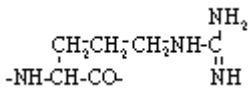
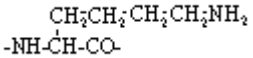
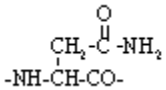
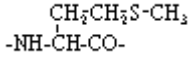
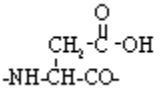
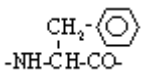
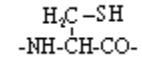
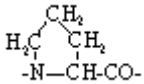
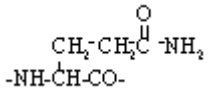
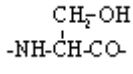
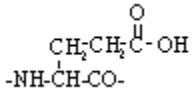
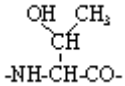
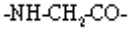
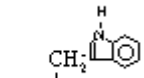
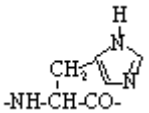
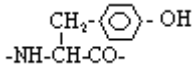
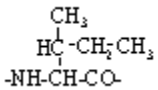
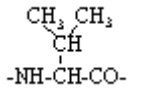
- pairing up blue and red tacks (positive and negative charges that neutralize each other)
- **and** pairing up green tacks that form disulfide bonds,
- **and** keeping all of the polar white tacks on the surface of the protein.

After everyone has folded their toober, the teacher can point out:

- Every toober had a different random sequence of tacks (amino acids) and therefore each toober (protein) folded into a different structure.
- Some sequences of tacks were more easily folded into a reasonable structure than others. In fact, the 30,000 proteins encoded by the human genome have been selected from an enormous number of possible amino acid sequences based on their ability to spontaneously fold into a stable structure that simultaneously satisfies these basic laws of chemistry.

For more suggestions about how to teach concepts of molecular structure and function, visit the MSOE Center for BioMolecular Modeling web site at www.rpc.msoe.edu/cbm and check out our summer course entitled ***Genes, Schemes and Molecular Machines***.

Amino Acid List

AA Name	AA	Code	Structure	AA Name	AA	Code	Structure
Alanine	Ala	A		Leucine	Leu	L	
Arginine	Arg	R		Lysine	Lys	K	
Asparagine	Asn	N		Methionine	Met	M	
Aspartic acid	Asp	D		Phenylalanine	Phe	F	
Cysteine	Cys	C		Proline	Pro	P	
Glutamine	Gln	Q		Serine	Ser	S	
Glutamic acid	Glu	E		Threonine	Thr	T	
Glycine	Gly	G		Tryptophan	Trp	W	
Histidine	His	H		Tyrosine	Tyr	Y	
Isoleucine	Ile	I		Valine	Val	V	

	Ala	Arg	Asn	Asp	Cys	Glu	Gln	Gly	His	Ile	Leu	Lys	Met	Phe	Pro	Ser	Thr	Trp	Tyr	Val
Acidic (negative)				D		E														
Basic (positive)		R							H			K								
Charged		R		D		E			H			K								
Neutral	A		N		C		Q	G	H	I	L		M	F	P	S	T	W	Y	V
Hydrophobic	A							G		I	L		M	F	P			W	Y	V
Hydrophilic (polar)		R	N	D	C	E	Q		H			K				S	T			

Amino Acid structure from www.ionsource.com

TOOBER VARIATIONS

There are many variations to the basic Toober folding exercise described in the "15 Tacks and a 4 foot Toober" handout. Each one can be used to emphasize a different point related to molecular structure. Examples of variations are described below.

Reversible Denaturation

Many proteins undergo reversible denaturation, by re-folding into their original shape (native structure) following their complete unfolding (denaturation) by heating.

1. Have students document the native shape of their folded protein with a digital photo.
2. Ask the students to unfold their protein and then re-fold it.
3. Check the refolded protein against the photo of the native structure.

Reverse Engineering

Some students will randomly generate a sequence of tacks that is very difficult to fold into a shape that simultaneously satisfies all 3 (or 4) laws of chemistry. This is a good "teaching moment" in that the teacher can use these examples to emphasize that such "proteins" would not be selected from the enormous pool of possible protein sequences.

How can students arrive at a perfectly optimized sequence of tacks that have been selected over evolutionary time to always fold into the same globular shape? **ANSWER:** By reverse engineering the sequence.

1. Have each group of students fold their toober into a compact globular shape without any tacks.
2. Have each group of students then add the tacks to the pre-folded toober, positioning them such that all of the "laws of chemistry" are satisfied in the folded structure.
3. Unfold the toober and document the sequence of tacks.
4. Have the students then re-fold the sequence into the original shape (see reversible denaturation, above).

The Effect of Mutations

Some mutations inactivate a protein by destabilizing its native shape.

1. Starting with the "reverse engineered" sequence of tacks as described above, mutate one of the hydrophobic amino acids (yellow tack) to a positively charged amino acid (blue tack).
2. Can the students fold this mutated sequence back into its native shape?

Share Your Variations! Let us know what other variations you use with your students, herman@msoe.edu