



# Toober Variations

There are many variations to the basic Toober folding exercise described in the student handout 1. 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 each student 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.

- a. Were you able to refold your protein into its native conformation? \_\_\_\_\_
- b. Don't feel bad. Although proteins can spontaneously refold into their correct shape following denaturation (unfolding), scientists are still trying to accurately predict the 3D structure of a protein from its primary sequence. This problem is commonly referred to as the "Protein Folding Problem." Google the "protein folding problem" and then list one web site that you found that provided a good explanation of this problem.  
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## 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 amino acids 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 sidechains.
2. Have each group of students then add the sidechains to the pre-folded toober, positioning them such that all of the "laws of chemistry" are satisfied in the folded structure.



## Reverse Engineering (continued)

3. Unfold the toober and document the sequence of amino acids.
4. Have the students then re-fold the sequence into the original shape (see reversible denaturation, above).

- Was it easier to refold this protein into its original shape than the one in the previous activity?

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## The Effects of Mutations

Some mutations inactivate a protein by destabilizing its native shape.

1. Starting with the “reverse engineered” sequence of amino acids as described above, mutate one of the hydrophobic amino acids (yellow sidechain) to a positively charged amino acid (blue sidechain).

- What effect do you think this mutation would have on the structure of the protein?

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- What effect do you think this mutation would have on the function of the protein?

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Share your variations. Let us know what other variations you use with your students.