Introduction:
Modern Protein Design

CS/CME/Biophys/BMI 371

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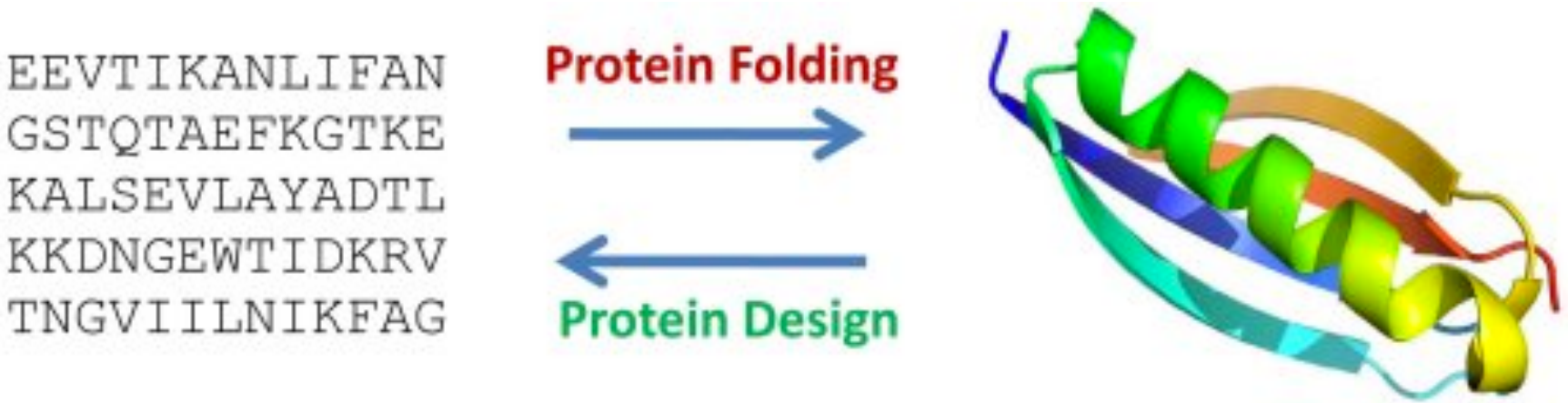
Protein design: problem definition

- Given the desired three dimensional structure of a protein, design an amino acid sequence that will assume that structure.
  - Of course, a precise set of atomic coordinates would determine sequence. Usually we start with a desired structure for the protein *backbone* (the atoms that all amino acids have in common, which form a "chain").
  - In many cases, we want the protein to have a particular *function*. We then start by hypothesizing structures that may have that function, and designing those.



http://www.riken.jp/zhangiru/images/sequence_protein.jpg

“Direct” approach doesn’t work

- “Direct” approach to protein design:
  - Given a target structure, search over all possible protein sequences
  - For each protein sequence, predict its structure, and compare to the target structure
  - Choose the best match
- This doesn’t work because:
  - It’s computationally infeasible
  - We’re not that good at predicting protein structure

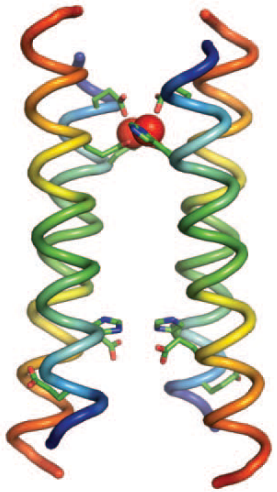
Practical protein design approaches dramatically simplify this problem by making a few assumptions

1. Assume the backbone geometry is fixed
2. Assume each amino acid can only take on a finite number of geometries (*rotamers*)
3. Assume that what we want to do is to minimize the energy of the target structure
   - Simply ignore all the other possible structures that we want to avoid

Each of these assumptions can be relaxed a bit

Papers for next Wednesday push the boundaries of traditional protein design

- Designing a protein that transports zinc ions through the cell membrane

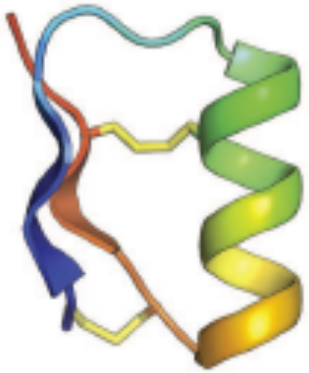


Joh et al., *Science* 2014

- Designing proteins that assemble into massive, ball-shaped complexes

Bale et al., *Science* 2016

- Designing peptides that are constrained by disulfide bonds



Bhardwaj et al., *Nature* 2016

Background material

- Protein design slides from CS/CME/BioE/ Biophys/BMI 279:
  - http://web.stanford.edu/class/cs279/lectures/lecture6.pdf
- "Computer-Based Design of Novel Protein Structures"
  - http://www.annualreviews.org/doi/abs/10.1146/annurev.biophys.35.040405.102046

Suggestions for presentations

- No more than 45 minutes total presentation time across all presenters
  - Most presenters spend at least one minute per slide, so you generally want no more than 45 slides total (across all presenters). **You may want fewer!**
- You need to explain the main idea of the paper
  - Often the figures in the paper are not sufficient to do this. You may need to make your own.
  - You should read the paper's supplementary information. You'll usually need to read other related papers as well.
- If you can include a demo or video, it's usually worthwhile