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PNA Midterm Exam

Due October 27, 2016 at the start of class

This is a take-home exam that is to be completed using publically available resources but without interactions with other people (e.g. faculty, older students, classmates). All of the work should be your own. Please turn in a hard copy of all of your answers at the beginning of class, with **your name on each page**. In addition to the paper copy, email an electronic version of your answers and your python scripts to anthony.veltri@jhmi.edu. For emails, please include "PNA midterm" in the subject line.

As this is a take-home exam, you are expected to be clear and also precise in presenting facts (e.g. don't write "about 2Å" for H-bond if you can look it up; likewise, don't just say "hydrogen bonding holds things together" but say with some detail how it does so).

1. Building blocks (10 pts):

    1a. The first proteins on Earth were presumably synthesized from raw materials available in the environment. Given the relatively high abundance predicted for β-alanine, what are some reasons why this amino acid was likely not selected as one of the 20 naturally occurring amino acids for proteins today?

    1b. Except for proline, why might the other 19 amino acids lack N-alkyl substitutions? What unique properties does proline have that may be advantageous for a folded protein?

2. What characteristics do folded protein cores have? Describe experimental results that support each property. Under what circumstances might a protein deviate from the characteristics you discuss? (10 pts)

3. In their 1998 JMB paper on the PNA course website, Plaxco & Baker conclude that "contact order" explains the folding kinetics of small, single domain proteins (10 pts).

    3a. Read the paper, and write a two sentence short summary of their thesis.

    3b. Based on our discussion of the kinetic barriers to protein folding, is their thesis physically plausible? Why or why not?

    3c. Describe an experiment that provides a critical test of their model.

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4. ClpA is a AAA+ protein unfoldase. Like ClpX, ClpA associates with ClpP protease to degrade misfolded or tagged cellular proteins (10 pts).

4a. How does the mechanism of ATP-dependent protein degradation allow ClpAP and ClpXP preferentially destroy misfolded proteins versus native proteins?

4b. ClpA forms a double-ring of ATPase domains, while ClpX makes a single ring. ClpAP degrades difficult substrates such as GFP much faster than ClpXP. However, ClpX is a faster intrinsic ATPase than ClpA. What else could explain why the double-ring ClpA is a stronger unfoldase than the single ring ClpX?

5. Based on our class discussion and readings, describe how the structure of the Sec translocon transports soluble, secreted proteins through the ER membrane, while allowing integral membrane proteins to insert into the lipid bilayer. (10 pts)

6. Describe five characteristic features of a protein-protein interface. How do reversible protein-protein interfaces differ from the cross-section of a folded globular protein? (10 pts)

7. Read the paper by Guskov et al. (PNAS 2012) on the CorA Mg^{2+} transporter. Answer the following questions (20 pts):

7a. How does the proposed mechanism of selective Mg^{2+} permeation by CorA differ from the mechanism of K^{+} permeation by KcsA? Support your answer with examples from the paper.

7b. The CorA Mg^{2+} transporter opens to allow the passage of Mg^{2+} ions when the intracellular Mg^{2+} concentration is low. How is CorA proposed to gate the flow of Mg^{2+} ions?

8. Write a python script to detect potential alpha-helical structures in a PDB file (use 1NJG) based on H-bonding distance criteria (don't worry about angles between H-bond donors and acceptors, just the distances). Have your program print out the protein sequence in single amino acid code (horizontal FASTA-like format) with an "H" above each letter that is helical and "-" above all other residues. How well does your program's identification agree with the secondary structure listed in the PDB header? (20 pts)