Protein Modeling Event

# National Exam

School Number: _____

Team Member 1: _____

Team Member 2: _____

Team Member 3: _____

| For Judges Use Only: | |
|---|---|
| Pre-Build Score: | |
| On-Site Build Score: | |
| Test Score: | |
| Tie Breaker: | |
| Total: | |
| Final Rank: | |

## Part I: Pre-Build (40% of total score)

Your Pre-Build Model should have been impounded the morning of the competition. You may pick up your Pre-Build model at the end of the competition after all models have been scored. Please pick up your model no later than 4pm. Unclaimed models will be thrown away.

## Part 2: On-Site-Build (30% of total score)

The workstation should have the On-Site Model Competition Environment open on the computer. Using the 152cm Mini-Toober provided, construct a model of the Cas9 – amino acids 1263-1339 of chain B of 4un3.pdb. The scale should be 2 cm per amino acid. A meter stick/ruler has been provided for you. Your Mini-Toober model of amino acids 1263-1339 of chain B of 4un3.pdb should include the following:

**A:** Four amino acids: Ile1270, Phe1324, Arg1333 and Arg1335 (use clips to connect amino acids to your Mini-Toober)

**B:** Blue end cap indicating the amino terminus (N-terminal end) of this region (amino acids 1263-1339)

**C:** Red end cap indicating the carboxylic acid terminus (C-terminal end) of this region (amino acids 1263-1339)

## Part 3: On-Site Exam (30% of total score)

The On-Site Exam consists of both multiple choice and short answer questions. You may use any materials provided at your work station as well as the five sheets you brought with you to answer these questions. You may NOT use the Internet to answer these questions.

There are ten multiple choice questions in the On-Site Exam (each worth 1 point for a total of 10 points). Clearly print the letter of the one BEST answer to each question in the blank provided for that question. Illegible answers will be incorrect.

There are also short answer questions in the On-Site Exam. The point value for each question is given in parentheses at the end of the question (20 pts total). The points for the tie-breaker questions (identified with ★ Tie Breaker) will be included in the final score but may be used to determine team placement in case of a tie.

# On-Site-Exam

## Multiple Choice Questions:

_____ 1. Which of the following amino acids contains an imidazole ring?

A. Proline (Pro)
B. Tyrosine (Tyr)
C. Tryptophan (Trp)
D. Histidine (His)

_____ 2. The CRISPR-Cas9 system in bacteria is akin to our body's

A. Digestive system
B. Immune system
C. Circulatory system
D. Respiratory system

_____ 3. CRISPR refers to repeated sequences located in the

A. Bacterial DNA
B. Viral DNA
C. Fungal DNA
D. Viral RNA

_____ 4. As proteins fold, amino acids with carbon-rich sidechains, like leucine and phenylalanine, are usually placed

A. on the surface of the protein
B. inside the protein
C. near positively charged residues
D. near polar residues

_____ 5. Which of the following proteins have not been used in genome editing?

A. ZFN
B. TALENs
C. CRISPR-Cas9
D. MHC

**For Judges Use Only**

Score for this page:

_____ 6. The Berlin Patient inspired which of the following strategies for treating HIV infection?

A. Disrupting the CCR5 gene
B. Blocking viral entry by interfering with the CD4-gp120 interaction
C. Blocking integration of proviral DNA into the host cell genome
D. Mimicking the reverse transcriptase enzyme substrate and binding to the active site

_____ 7. To direct a nuclease to a statistically unique DNA sequence on the human genome, it must be able to recognize a sequence that is at least

A. 10 base pairs long
B. 16 base pairs long
C. 32 base pairs long
D. 5 base pairs long

_____ 8. The CRISPR sequences are recognized by

A. Zinc finger domains
B. TALE repeats
C. Guide RNA
D. Leucine zippers

_____ 9. What is the name of the chemical reaction that catalyzes the cleavage of a peptide bond?

A. Oxidation
B. Reduction
C. Dehydration
D. Hydrolysis

_____ 10. Which of the following statements is NOT true about the FokI enzyme:

A. It is a bacterial restriction endonuclease
B. It recognizes specific DNA sequences and makes single stranded breaks
C. It is derived from *Flavobacterium okeanokoites*
D. It has DNA binding and nuclease domains

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Score for this page:

# Short Answer Questions:

1. The CRISPR associated protein Cas9 is now being used as a molecular tool for genome editing. (4 pts)

   "CRISPR" is an acronym for what phrase? (1pt)

   What is the role of Cas9 in genome editing? (2pts)

   In a cell, what happens to a gene that has been cut by a genome editing system? (1 pt)

2. The structure of Cas9 that you are modeling on-site includes a target DNA strand, non-target DNA strand and guide RNA. (4 pts) ★ Tie Breaker

   How is the guide RNA made and what role does it play in this gene-editing method? (2 pts)

   What is the difference between the structures of DNA and RNA sugars? (1pt)

   What is the difference between the DNA and RNA bases? (1 pt)

3. Genome editing requires bio-molecular tools to specifically recognize a target sequence on the genome and cut it in a precise way. (4 pts)

   List 2 molecular tools other than the CRISPR Cas9 system that are available for genome editing. (2 pts)

   In what way is the CRISPR-Cas9 system different from the genome editing tools listed above (1 pt)

   The Cas9 protein needs to be engineered to add a specific signal so that it can be transported into the nucleus. What is this signal called? (1 pt)

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Score for this page:

4. Four amino acid side chains -- Arg1333 , Arg1335, Phe1324 and Ile1270 – were added to your on-site model of a region of the Cas9 protein. (4 pts) ★ Tie Breaker

   How might Phe1324 and Ile1270 contribute to the structure and function of the Cas9 protein? (2 pts)

   How do Arg1333 and Arg1335 contribute to the structure and function of the Cas9 protein? (2 pts)

5. In the last three decades, a number of different strategies have been developed to treat HIV infection. Current research is focused on finding cures and a vaccine against HIV (4 pts).

   The current FDA approved drugs to treat HIV disrupt the HIV life cycle. Name three HIV Viral Enzymes that are targeted by these drugs. (1.5 pts)

   Name two other types of drugs used to treat HIV and describe how each of theses currently approved classes of drugs block the HIV life cycle. (1 pt)

   List one genome editing approach and its target that is currently being tested for providing a functional cure for HIV infection and explain how it works. (0.5 pts)

   List one genome editing approach and its target that can completely cure an HIV infection. (1 pt)

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Protein Modeling Event

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# On-Site-Exam

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C. Tryptophan (Trp)
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A 3. CRISPR refers to repeated sequences located in the

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A. on the surface of the protein
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B. Reduction
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# Short Answer Questions:

1. The CRISPR associated protein Cas9 is now being used as a molecular tool for genome editing. (4 pts)

   "CRISPR" is an acronym for what phrase? (1pt)
   Clustered Regularly Interspaced Short Palindromic Repeat

   What is the role of Cas9 in genome editing? (2pts)
   Cas9 binds to a complex of guide RNA (or CrRNA:TraCrRNA) and Target DNA (1 pt) and introduces a double stranded break in the target DNA (1 pt).

   In a cell, what happens to a gene that has been cut by a genome editing system? (1 pt)
   It is repaired using either non-homologous end joining (NHEJ) (0.5pts) or homology dependent repair (HDR) (0.5pts)

2. The structure of Cas9 that you are modeling on-site includes a target DNA strand, non-target DNA strand and guide RNA. (4 pts) ★ Tie Breaker

   How is the guide RNA made and what role does it play in this gene-editing method? (2 pts)
   In the CRISPR-Cas9 system the guide RNA binds to the target DNA and directs the Cas9 nuclease activity (1 pt). It is made as a mimic of the crRNA:tracrRNA complex by joining these sequences into a single stranded RNA with a linker RNA (1 pt).

   What is the difference between the structures of DNA and RNA sugars? (1pt)
   DNA has deoxyribose sugar (0.5 pts) while RNA has ribose sugar (with extra oxygen atom) (0.5 pts)

   What is the difference between the DNA and RNA bases? (1 pt)
   DNA has the nucleic acid bases A,G,C,T (0.5 pts) while RNA has A,G,C,U (0.5 pts)
   Full points may also be awarded if the answer only discusses T Vs U in DNA Vs RNA respectively.

3. Genome editing requires bio-molecular tools to specifically recognize a target sequence on the genome and cut it in a precise way. (4 pts)

   List 2 molecular tools other than the CRISPR Cas9 system that are available for genome editing. (2 pts)
   1. Zinc Finger Nuclease (ZFN) (1 pt)
   2. Transcription Activator Like Effector Nucleases (TALENS) (1 pt)

   In what way is the CRISPR-Cas9 system different from the genome editing tools listed above (1 pt)
   Cas9 recognizes the target DNA via a guide RNA (0.5 pts) while the ZFN and TALENS recognize target DNA through specific protein domains/motifs (0.5 pts).

   The Cas9 protein needs to be engineered to add a specific signal so that it can be transported into the nucleus. What is this signal called? (1 pt)
   A lysine rich (0.25 pts) Nuclear Localization Signal or NLS (0.75 pts)

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Score for this page:

4. Four amino acid side chains -- Arg1333 , Arg1335, Phe1324 and Ile1270 – were added to your on-site model of a region of the Cas9 protein. (4 pts) ★ Tie Breaker

   How might Phe1324 and Ile1270 contribute to the structure and function of the Cas9 protein? (2 pts)
   These sidechains are hydrophobic in nature – and are closely packed in the inside of a sub-domain of the protein. Hydrophobic interactions between these sidechains and other hydrophobic sidechains in this region stabilize the structure of the protein. (2 pts)

   How do Arg1333 and Arg1335 contribute to the structure and function of the Cas9 protein? (2 pts)
   These two basic sidechains (1 pt), interact specifically with the GG dinucleotide of the PAM sequence of the guide RNA (1 pt) – binding it to the Cas9 protein.

5. In the last three decades, a number of different strategies have been developed to treat HIV infection. Current research is focused on finding cures and a vaccine against HIV (4 pts).

   The current FDA approved drugs to treat HIV disrupt the HIV life cycle. Name three HIV Viral Enzymes that are targeted by these drugs. (1.5 pts)
   1. Reverse Transcriptase (0.5 pts)
   2. Protease (0.5 pts)
   3. Integrase (0.5 pts)

   Name two other types of drugs used to treat HIV and describe how each of theses currently approved classes of drugs block the HIV life cycle. (1 pt)
   1. Entry inhibitors (0.25 pts) block interaction of the CD4-gp120 complex with CCR5 (0.25 pts)
   2. Fusion inhibitor (0.25 pts) blocks conformational changes in gp41 and fusion of viral and host cell membranes (0.25 pts).

   List one genome editing approach and its target that is currently being tested for providing a functional cure for HIV infection and explain how it works. (0.5 pts)
   CCR5 disruption (0.25 pts) by ZFNs can prevent reinfection in infected individuals (0.25 pts)

   List one genome editing approach and its target that can completely cure an HIV infection. (1 pt)
   The CRISPR-Cas9 system (0.5 pts) could seek and edit out integrated HIV proviral DNA (0.5 pts) resulting in a cure for HIV.

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Score for this page:

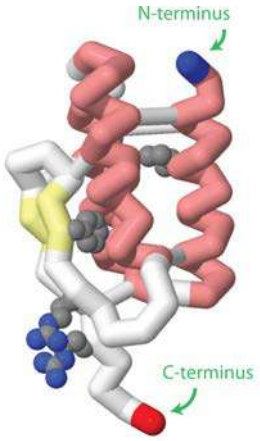
Protein Modeling Event

# Guide to Scoring the National On-Site Model

**For Science Olympiad 2015 National Competition**

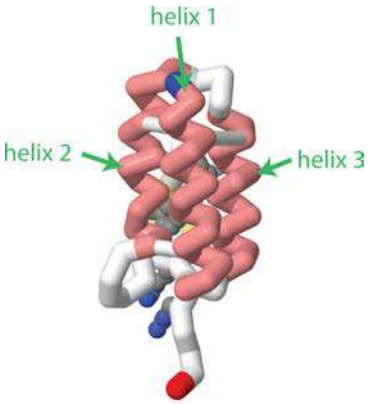
These instructions are to help the event supervisor and scoring judges use the rubric developed by the RCSB PDB and MSOE for scoring the 2015 Science Olympiad pre-build models at the national event. Each category on the rubric is addressed within these instructions and is accompanied by a short description and picture, where appropriate. The guide is based on a model based on PDB entry 4un3.pdb chain B residue 1263-1339. A 3D model of the same is also available for scoring.

1. **Blue cap on the N-terminal amino acid** (1 pt) The N-terminus is on a helix in the model. The model should have a blue cap, indicating the N-terminus of the polymer as shown in the figure to the right.



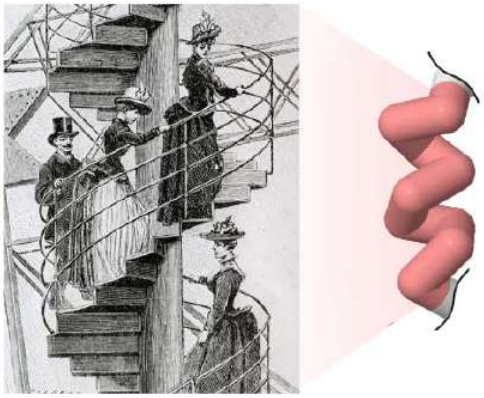

2. **Red cap on the C-terminal amino acid** (1 pt) The model should have a red cap indicating the C-terminus of the polymer at the end of a beta-strand-containing portion of the model as shown in the figure to the right.

3. **The N- and C-termini are on opposite ends of the model** (1 pt)

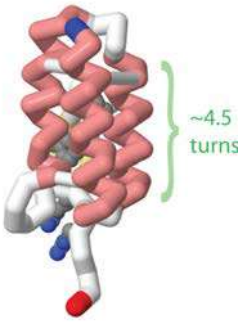



4. **Model has 3 helices** (3pts, 1pt each) Starting form the N-terminus, there are 3 helices with loops in between. These helices in the model should be clearly identifiable as shown in the figure to the right. The helices are colored pink in the figure.

5. **Alpha helices are right-handed** (3 pts, 1pt each) In order to receive the points check that each alpha helix in the model is right handed. For each helix find one of the ends of the helix and imagine that the helix is a spiral staircase. Pretend that you are climbing that staircase and you need to have a hand-rail and the helix is the hand-rail, which is always on the outside edge of the staircase. If you would put your right hand on the toober as you go up the staircase, you have a right-handed helix. If you would put your left hand on the toober, you have a left-handed helix and the modeled helix would not receive credit. The helix should also be evenly spaced. Being right handed and evenly spaced will earn the model 1 point for that helix. A total of 3 pts can be awarded for the 3 helices.

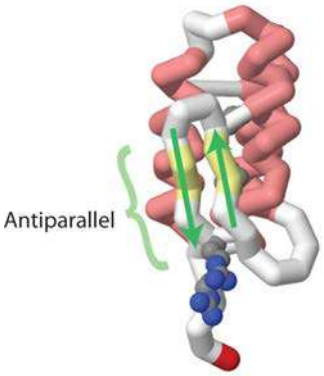


6. **Each of the 3 helices have ~4.5 turns** (6pts, 2 pts per helix) While the1st and 3rd helices in the model has ~4 and ¾ turns, the second one has ~4 and ¼ turns. As long as this is approximately correct the model can receive full points. If there are <=3 turns or >5 turns in any of the helices 0.25 points may be deducted for each extra or fewer turn.

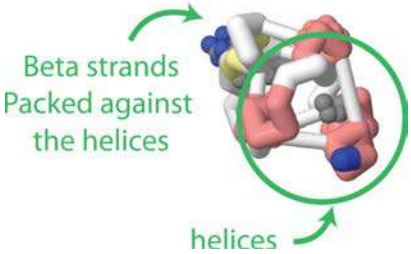



7. **The model has 2 beta strands** (2 pts, 1 pt each) These strands lie adjacent to each other, are antiparallel and form a beta hairpin.

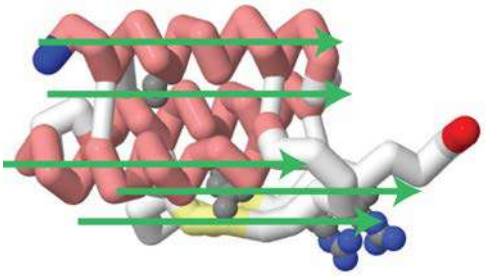
8. **Each beta strand is ~2 residues long** (2 pts, 1 pt each) The beta strand part in each of the strands is very short (2 residues) and should be appropriately marked/folded with pleats etc. so that they are clearly recognizable. If the beta strand region marked is 3 or more residues – points may be deducted (0.5 per residue).




9. **The beta strands (hairpin) is packed on the three helices to form a compact structure** (1 pt) The 3 helices are on one side while the beta strands are on the other as shown in the figure to the right.

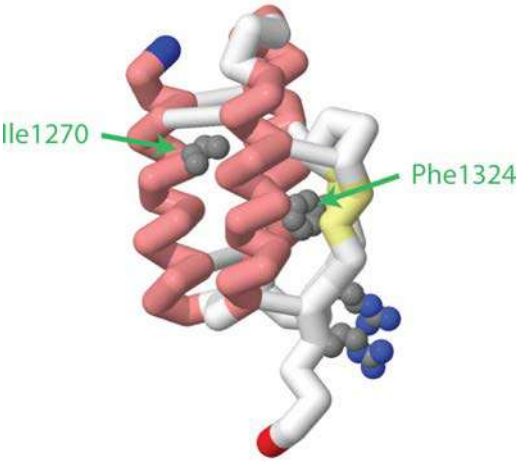



10. **The helix axes and strand axes are ~parallel to each other** (1 pt, 0.2 pts each) View the model from the side to see the helix and strand axes. They should all be ~parallel as shown in the figure. For each secondary structural element that is not in this orientation 0.2 pts may be deducted.



11. **The residue Ile1270 is located on the N-terminal helix.** (1 pt) Note that this residue is located in the 3rd turn of the N-terminal helix. The sidechain of this residue is shown in the figure to the right.

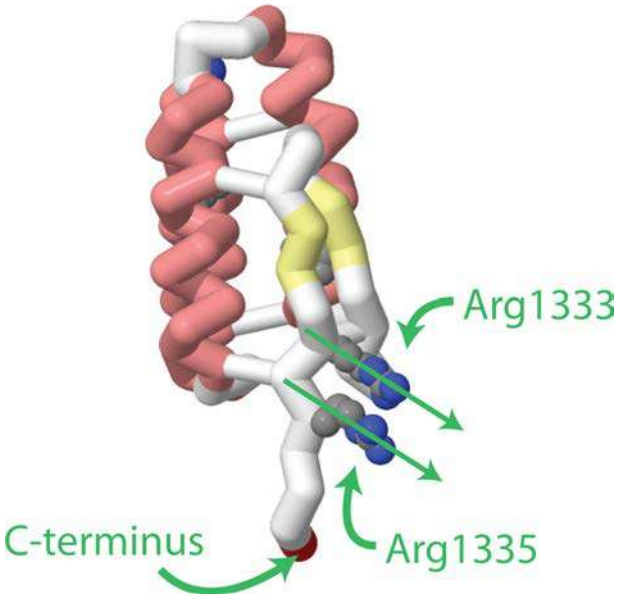
12. **The residue Phe1324 is located on the first beta strand in the model.** (1 pt)




13. **Sidechains of the Phe1324 and Ile1270 point towards the core of the model** (1 pt) The sidechains are both hydrophobic and should point towards the hydrophobic core.

14. **The sidechains R1333 and R1335 are both located on the C-terminal beta strand.** (2pts, 1pt each) To score points here the Arg residues must be positioned in the coil region beyond the beta strand region.

15. **Sidechains of R1333 and R1335 directed away from the helices and point towards C-terminal end** (2pts, 1 pt each) The R1333, and 1335 are pointing away from the hydrophobic core region of the model and also away from the helices. They are pointed in the direction of the C-terminus. See figure. Any residue that is not pointing in the direction shown will not receive credit.




16. **Side chains of residues (R1333 and R1335) stack on top of each other** (2 points) Both of these residues need to be oriented in a way that allows them to bind to the PAM region of the RNA adjacent to the model and should therefore be stacked on top of each other as shown in the figure to the right.

Protein Modeling Event

# Guide to Scoring the National Pre-Build Model

**For Science Olympiad 2015 National Competition**

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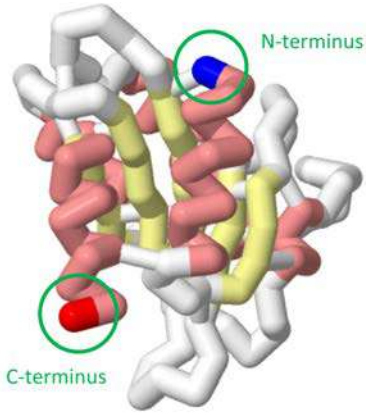
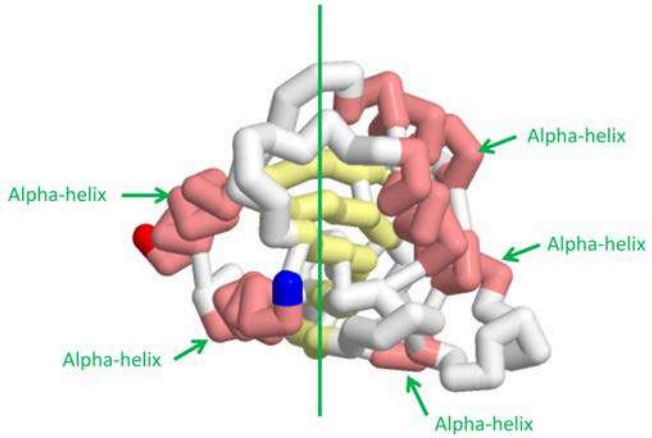
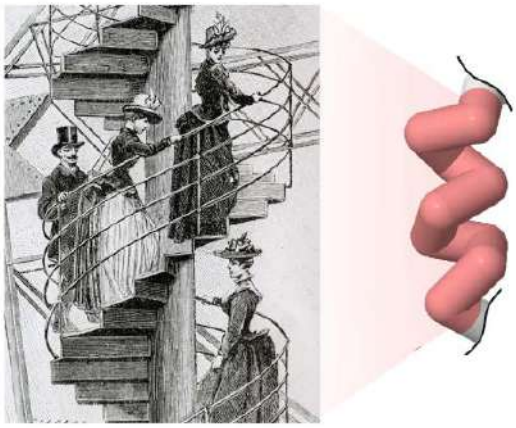



1. **Blue cap on the N-terminal amino acids of Chains A** (0.5 pts). The model should have a blue cap, indicating the N-terminus of the polymer (Chain A) as shown in the figure to the right.

2. **Red cap on the C-terminal amino acids of Chains A** (0.5 pts). The model should have a red cap, indicating the C-terminus of the polymer (Chain A) as shown in the figure to the right.

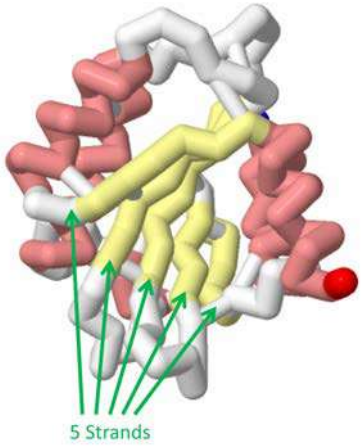
3. **Model has 5 helices** (2.5 pts, 0.5 pts each). The model should have 5 helices – 2 helices on one side of the beta sheet (1 N-terminal, 1 C-terminal,) 2 other helices on the other side along with a smaller helix. The helices are colored pink in the figure below and to the left. Each helix over 5 helices should deduct 0.5 points.



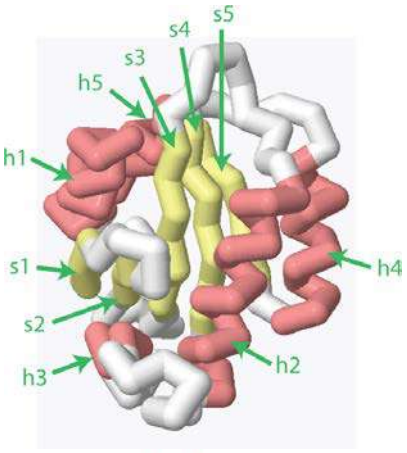



4. **Alpha helices are right-handed** (2.5 pts, 0.5 pts each). In order to receive the points, check that the alpha helices in the model are right handed as shown in the figure above and to the right. Imagine that each helix is a spiral staircase. As you climb the staircase, your right hand should be on the outside hand-rail. If you would put your right hand on the mini toober as you go up the staircase, you have a right-handed helix. If you would put your left hand on the mini toober, you have a left-handed helix and the modeled helix would not receive credit. The helix coils should also be evenly spaced. Being right handed and evenly spaced will earn each helix in the model 1 point – a total of 5 pts.

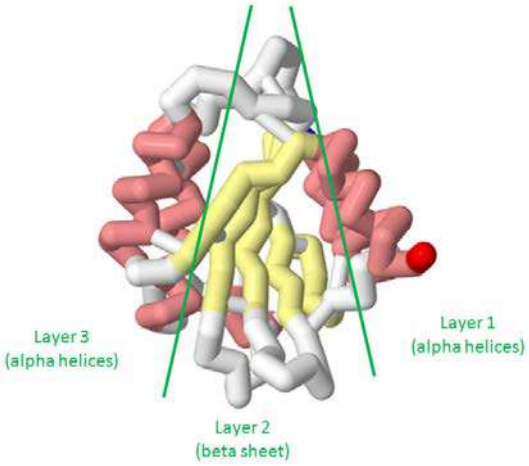
5. **Model has 5 β-strands** (2.5 pts, 0.5 pts each). There should be 5 β-strands in the structures (each between 4 and 7 amino acids long). These strands need to be clearly distinguishable from loops; there may be some slight 'zig-zag' folding of the toober to indicate the up-and-down positioning of the amino acids. Alternately, teams might color-code their beta strands to distinguish them from loops or write on the toober indicating the location of the β-strands. The event supervisor should not have to guess what a beta-strand is within the model. If there are more than 5 β-strands in the model, 0.25 pts should be deducted for each extra strand. For example, if the model has 6 β-strands, the model should receive 2.25 points, rather than the full 2.5 points.



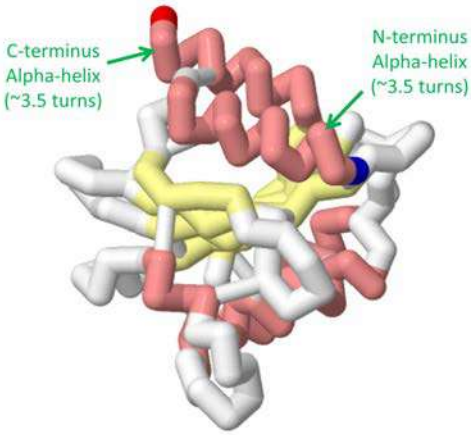

6. **Secondary structural elements order (N- to C-terminus)**: (2.5 pts, 0.25 pts each) Follow the chain from the N- to C-terminus. The order of secondary structural elements is helix1-strand1-strand2-strand3-helix2-helix3-strand4-helix4-strand5-helix5 or h1-s1-s2-s3-h2-h3-s4-h4-s5-h5 (where h=helix; and s=strand).




7. **Model has three layers** (1.5 pts, 0.5 pts per layer). Model can be viewed as having three distinct layers. If you hold the model so that the center beta sheet is approximately perpendicular to the floor, it should be sandwiched between two layers, each with only helices as seen in the physical model and the figure to the right.

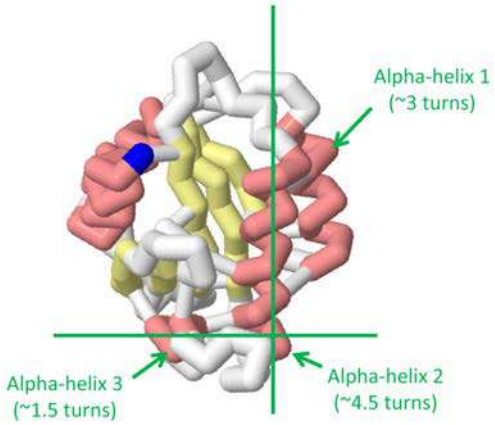



8. **The N- and C-terminal helices are in the same layer (layer 1)** (0.5 pts). The N- and C-terminal helices should form part of the same helical layer in the model. These termini should be located at diagonally opposite ends of the layer. Each of the N- and C-terminal helices are ~3.5 turns long as shown in the figure below and to the left. Deduct 0.25 points for each helix if they have less than 3 or more than 4 turns.

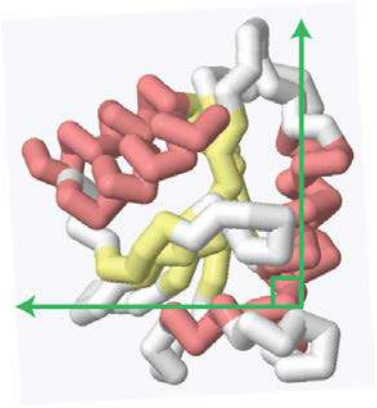


9. **The second layer has 1 β-sheet** (1 pt). The β-sheet forms the second layer of the protein model. The 5 strands in the sheet are somewhat twisted but in the same layer. Please refer to the physical model and the figure on the previous page. The strands in the sheet are colored yellow. If the model has more than one β-sheet, then deduct 0.5 pt for each additional sheet. For example, if the model has two β-sheets, the model should receive 0.5 pts, rather than the full 1 pt.

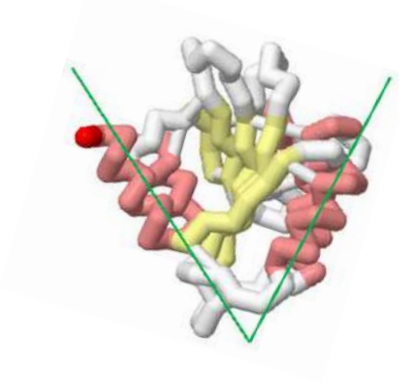
10. **The third layer has the remaining 3 helices (including 1 very short one)** (1.5 pts). There are 2 helices in this layer that are ~3 and ~4.5 turns long (0.25 pts each). Their helical axes are parallel to each other (0.5 pts). In addition, there is a short helix of ~1.5 turns (0.25 pts) that has a helical axis almost perpendicular to that of the other 2 helices in this layer (0.25 pts). To receive points the length of helices in the model and their relative orientations should match that listed here. See figure.



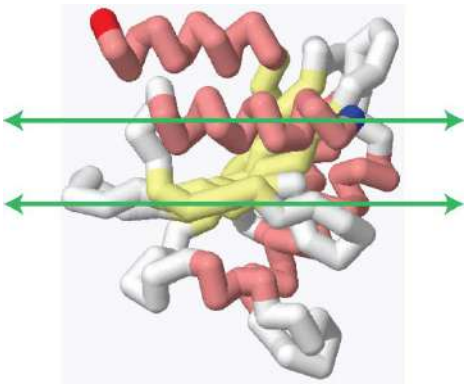

11. **Helix axis of the short helix is perpendicular to that of the other two in that layer** (0.5 pts). The figure on the right shows how the helical axes of the two longer helices in layer 3 are perpendicular to that of the short helix.



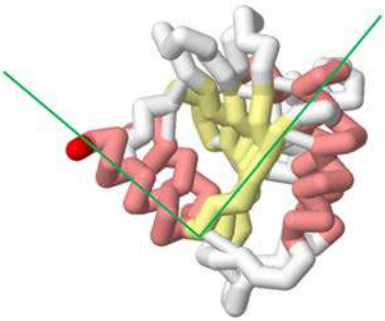
12. **The 2 helix-containing layers (Layers 1 and 3) form a V-shape** (0.5 pts). Hold the model so that the central beta sheet is perpendicular to the floor and the C-terminus points upwards. The layers 1 and 3 (containing the helices) are not parallel but form a V-like shape as shown in the figure to the right.



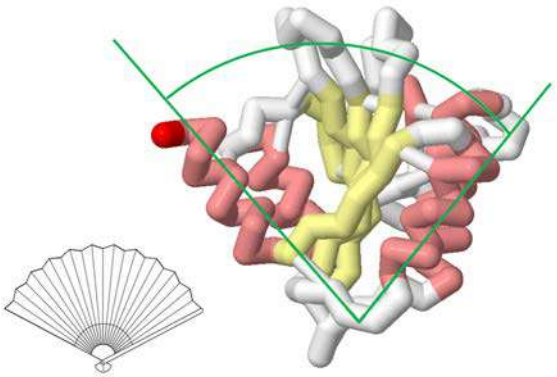
13. **Axis of the N-terminal helix and the first beta strand are parallel** (0.5 pts). Hold the model as shown in the adjacent figure and note that the N-terminal helix axis should be parallel to the first beta strand.



14. **The C-terminal helix and the last beta strand form a V shape** (0.5 pts). Hold the model so that the central beta sheet is perpendicular to the floor and the C-terminus points upwards. The C-terminal helix axis and the last beta strand form a V- shape as shown in the figure to the right.

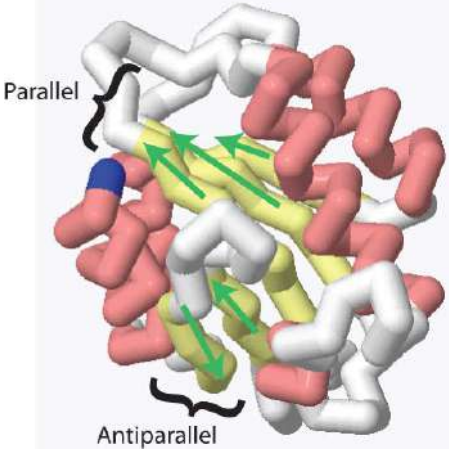


15. **The overall shape of the protein domain is like a Chinese or Japanese fan** (0.5 pts). Hold the model with the N-terminal helix pointing vertically up (N-terminus at the top), all of the secondary structures (alpha helices and beta strands) should spread out like a hand fan.



16. **The first 2 strands of the beta sheet are antiparallel** (2 pts). Follow the direction of the beta strands starting from the N-terminal helix. The strands 1 and 2 are antiparallel or oriented in the opposite directions

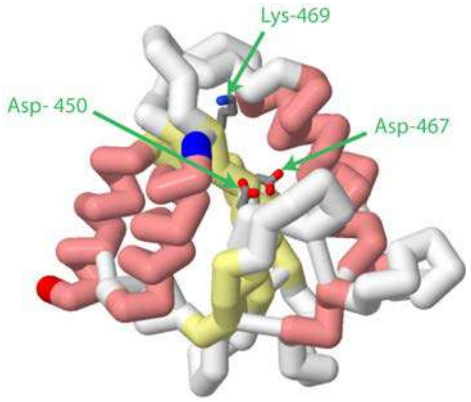
17. **The last 3 beta strands in the beta sheet, are parallel** (3 pts). In the remaining 3 strands of the beta sheet the N- to C- direction is the same making them parallel. Follow the polymer chain to determine the strand orientation as shown in the figure to the right. Deduct one point for each strand that is not shown in the correct N- to C- direction.



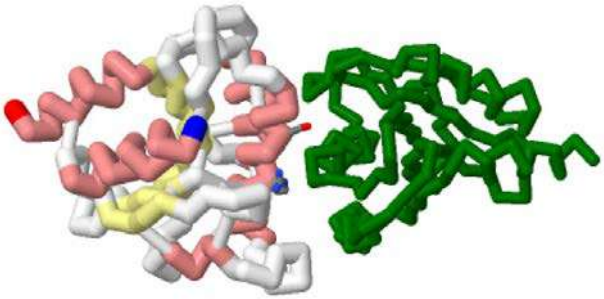

18. **Students submitted a 3x5 note card with explanation** (0.5 pts). The 3x5 card submitted with the model should describe the model in terms of what additional features have been added to the model so that the judge is not left guessing what the model represents.

**19. Creative Additions** (4 pts each; max of 16 pts) possible additions include:

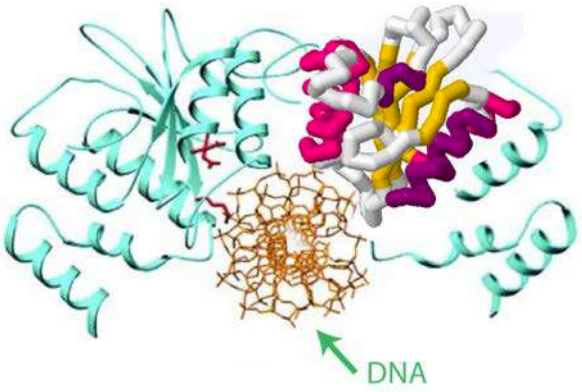
a. Active site amino acids (Asp- 450, Asp-467, and Lys-469). The enzyme active site is described in the primary citation for the PDB entry (2fok). These side chains may be highlighted as active site residues as shown in the figure to the right. Inclusion of side chains for these residues will receive credit (1 pt each). An additional 1 pt can be awarded for all three residues being highlighted (making the maximum possible points for this feature to be 4 points). If totally different residues are shown as active site residues 0.5 pts should be deducted for each incorrect residue.



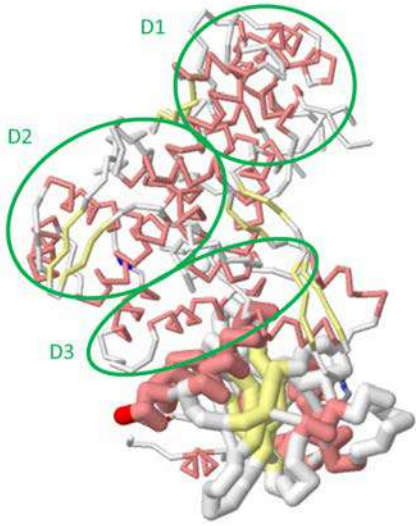

b. Addition of a 2nd catalytic domain of FokI. The Fok I enzyme functions as a dimer. The second catalytic domain may be shown as the green domain in the figure to the right.



c. Possible DNA binding location (with or without DNA). The model may indicate the possible DNA binding region – either with labels or by including a DNA model. The approximate location of the DNA in the model is shown in the figure to the right from the primary citation of PDB entry 2FOK.

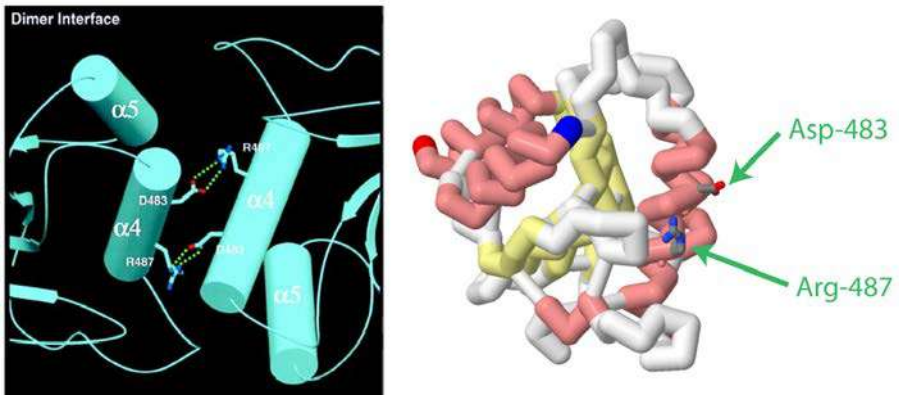



d. DNA binding domains of FokI shown. The model may show additional domains representing the DNA binding domains of the Fok I enzyme. See the D1, D2 and D3 domains in the figure to the right.



e. DNA binding domains of zinc finger, TAL effector or other DNA localization domain shown. Instead of the DNA-binding domains D1-D3, the model may also highlight the structure of 3 zinc fingers representing the zinc finger nuclease. The 3 zinc fingers should at least be bound in the region where the Fok I DNA-binding domain is located to receive credits.


f. Amino acid side chains involved in dimerization of catalytic domain shown. The residues responsible for the dimer interaction (Asp-483 bonds with Arg-487) may also be shown as seen in the image below. Inclusion of any one or all of these residues will receive a 4 pts credit. If totally different residues are listed as active site residues no points should be awarded.




g. Additional features not described above. Any additional feature with functional relevance that the judges think is appropriate can earn 4 pts each. If two or more such additional features (i.e. features not listed above in a through f, are highlighted, a maximum of 8 points may be awarded based on the judge's and event supervisor's discretion. To get a full score of 16 pts in this section, the remaining points should be earned based on the features listed in a-f.

**20. Additions to model are appropriate to function** (0.5 pts). Credit should be awarded to those models that meet the following criteria:

- Model has creative additions - Models that are just the toober will not receive credit
- Additions should be appropriate to the function of the protein - Models that have ALL side chains displayed should not receive credit since this suggests that the team did not recognize the significance of a select few amino acids to the protein's function.
- All highlighted amino acids (side chains or location on the backbone), additional domains, or molecules (e.g. DNA. RNA or partner proteins) should have some functional or structural significance, otherwise no points should be awarded.