

Hands-On Fifteen Molecular Modeling

In this Hands-on Exercise, you will learn how to:

1. Computationally mutate residues in a protein.
 2. Create a homology model of a protein domain using Swiss-MODEL.
 3. Choose the best structure, when more than one is available.
1. Download ho15ex1.pdb from <http://salilab.org/~nkhuri/Rabat2013>
 2. Start the UCSF Chimera viewer (close current Chimera sessions) and open ho15ex1.pdb. What secondary structural elements can you identify in this structure?
 3. Change the representation of the molecule from ribbon to all atoms. Select Val27 residue and mutate it to Trp. Select “Tools”, “Structure Editing”, “Rotamers” and click on “OK”. You should see that there are many possibilities for fitting a Trp to this structure. Select the most probable rotamer (the one with the highest probability) in the table and click on “OK”.
 4. In the previous step, we replaced a valine residue with a bulkier (bigger) residue. To see if this mutation resulted in any steric clashes with other residues, make sure that Trp27 is selected, then go to “Tools”, “Structure Analysis”, “Find Clashes/Contacts”. Click on the “Designate” button at the top and check the “Color” box under “Treat clash/contact atoms”. Run the tool. Which residues clash with Trp27?
 5. Steric hindrance may be relieved by performing energy minimization of the protein structure. Select “Tools”, “Structure Editing” and “Energy minimization”. Change the “Steps” to 500 and accept all other default settings. You can see the minimization process in your Chimera window”. Upon completion of this process, verify that any steric clashes for Trp27 were resolved. If not, you can repeat the minimization procedure.
 6. Mutate Gly12 to Val and perform energy minimization to relieve the steric clashes introduced by the mutation.
 7. In the next steps, we will perform comparative modeling of protein structures. Visit <http://swissmodel.expasy.org/> and use the website's navigation tools to complete the following:
 - a. Register
 - b. Collect the assigned password from your email
 - c. Use this password to login to Swiss-Model

8. Copy of one the FASTA sequences (easy_target_1.fasta or easy_target_2.fasta or easy_target_3.fasta) from <http://salilab.org/~nkhuri/Rabat2013>
9. In your workspace (logged in to <http://swissmodel.expasy.org/>) click "Modeling" then "Automated Mode". Enter your email address. Enter a sensible title in the "Project Title:" box. Paste your FASTA sequence into the large box that says "Provide a protein sequence ..." and click on the "Submit Modeling Request" button. It may take several minutes to return a result as you're relying on the server to do a lot of work for you.