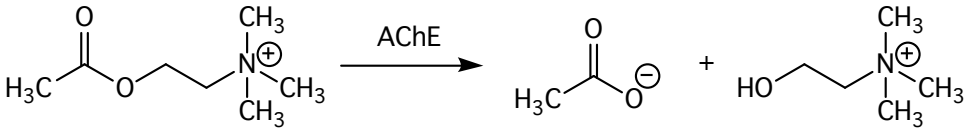
Study Question 5: Acetylcholinesterase

Acetylcholinesterase catalyses the hydrolysis of the neurotransmitter acetyl choline. This is one of the fastest reactions known. The (unbalanced) reaction is shown below.



acetyl choline

k_{cat} ~ 25K/sec

As a warm-up, you might try drawing the non-enzymatic mechanism, using HO^- or H_2O as a reactant.

The files you need for this question are available on the main course web site (download AChE.zip and unstuff it).

This first set of questions concerns file AChEv1.py (created from PDB entry 2ace).

1. What substrate is in the active site? Draw its structure. What mechanistic intermediate does this correspond to?
2. Locate the catalytic triad, and give the identifiers/numbers for each residue.
3. What residue(s), and what intermolecular force(s), appear to stabilize the quaternary nitrogen?
4. There are several backbone pieces which stabilize the so-called "oxyanion" hole. Draw a picture of these interactions, and give identifying names and numbers.
5. Describe the location of the active site relative to the entire structure.

   Switch to file AChEv2.py
6. Four additional amino acid side chains have been included in this view (relative to the previous structure). What are they (name and number), what do they have in common, and what role do they appear to be playing?
7. With your answer above in mind, what limits are placed on the design of an inhibitor for AChE? Answer by drawing and annotating the structure of acetylcholine.

   Switch to file AChEv3.py (derived from PDB entry 2c58).
8. This file has most of the active site side chains stripped out for clarity. What molecule(s) is(are) at the active site? Draw the structures.
9. This structure is part-way along the reaction pathway. Describe where is it stuck. What about the structures you identified just above is mechanistically consistent with where the reaction is stuck?

   Switch to file AChEv4.py (derived from PDB entry 1amn). This structure has an inhibitor bound to AChE.
10. Examine the side chains near the inhibitor. What is different about these particular side chains?
11. Examine serine 200 which is the active site serine. What's "wrong" with it?
12. With your answer above in mind, draw the structure of the inhibitor.
13. This inhibitor is "non-hydrolyzable." What does this mean? Explain mechanistically.
14. Why is this inhibitor reactive? Explain.