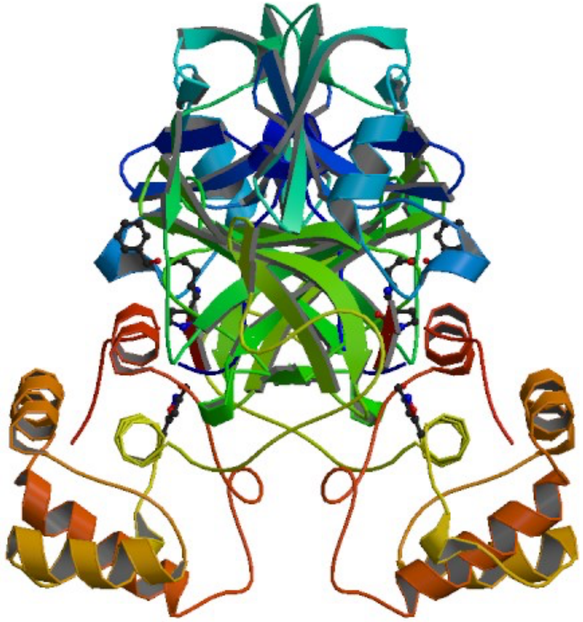
What is known about 3cl^{pro}?

- There is no proven cure for COVID-19
- The 3C-like protease (3cl^{pro}), also known as the main protease (M^{pro}),
  - is a key part of the life cycle of the COVID-19 virus
  - cleaves polyproteins to allow the virus to assemble
- 3cl-pro is a possible target for structure-based drug design
  - Proteases with similar function are established drug targets in other viruses, like HIV
  - A high-resolution (2.16 Å) structure in complex with an inhibitor has been solved and deposited into the protein data bank as 6LU7 [1]
  - The enzyme is inhibited by several compounds with a micromolar IC_{50} [1]



Previous modeling of 3cl^{pro}

- Molecular dynamics simulations that suggest high flexibility [2]
- Molecular docking suggests that
  - HIV protease inhibitors including lopinavir can be repurposed against the COVID-19 enzyme [3, 4]
    - there are clinical trials of using Kaletra (lopinavir/ritonivir) against COVID-19
  - Natural products may inhibit the enzyme [3]
- Binding free energy calculations
  - can be used to refine docking hits to identify the most promising repurposing candidates
  - may inform dosing recommendations in clinical trials
  - can model fluctuations of the enzyme in the presence of different known inhibitors
- To start this demonstration, I used AutoDock Vina to dock the FDA approved drugs database and known inhibitors [1] against 3cl-pro. Then I prepared the some systems for YANK.