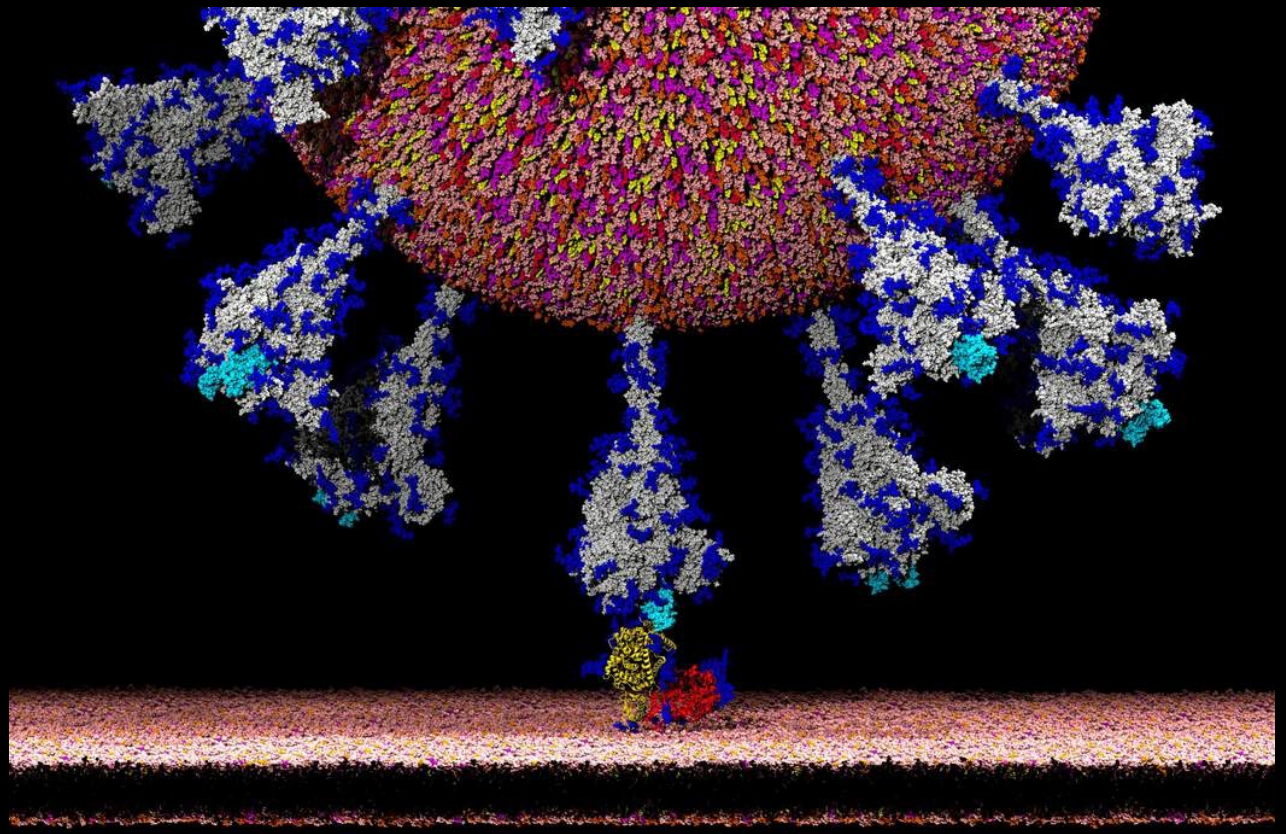
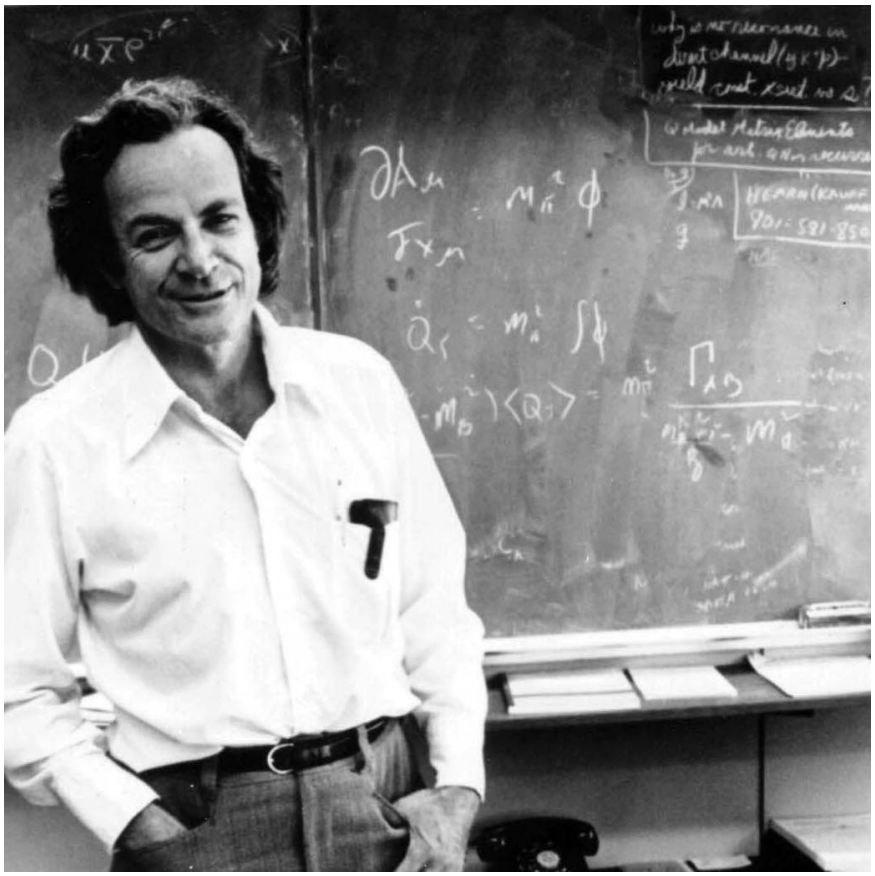
Computer simulations to study SARS-Cov-2 proteins

April 30, 2021



Lorenzo Casalino, Amaro Lab (*Colloquium Feb 5*). https://www.nytimes.com/interactive/2020/health/coronavirus-unveiled.html

INTRODUCTION

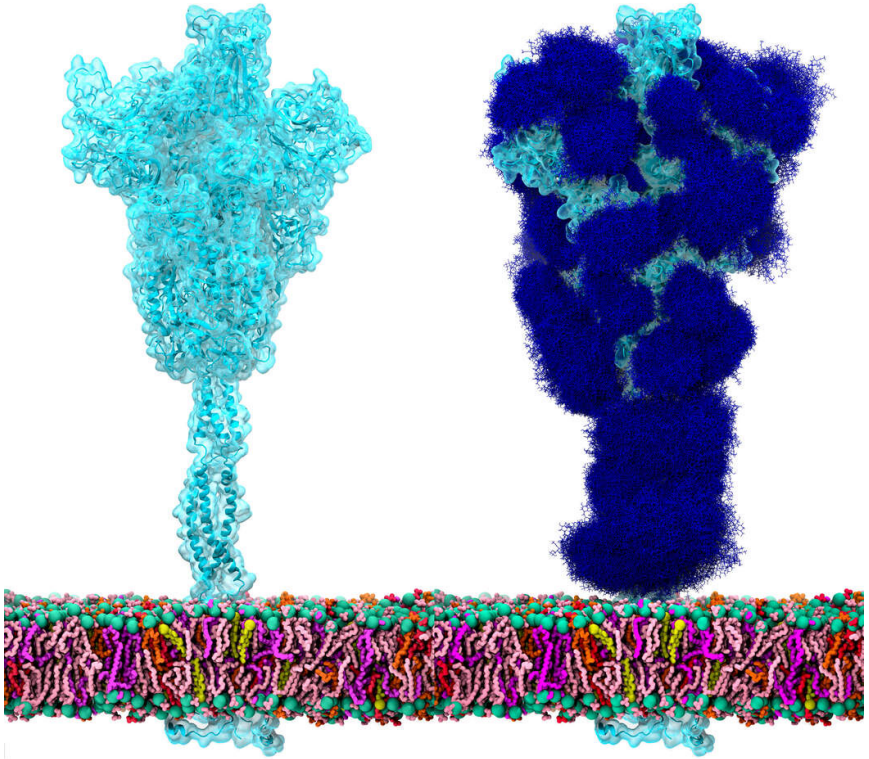


"...if we were to name the most powerful assumption of all, which leads one on and on in an attempt to understand life, it is that all things are made of atoms, and that everything that living things do can be understood in terms of the jigglings and wigglings of atoms."
– Feynman Lectures in Physics, 1964

"…all things are made of atoms" = Chemistry

"…jigglings and wigglings" = Physics

USING COMPUTERS TO SOLVE PROBLEMS IN BIOCHEMISTRY



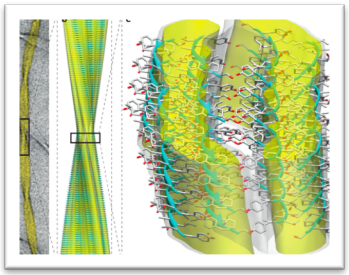
Lorenzo Casalino, Zied Gaieb (Amaro Lab). https://www.nytimes.com/interactive/2020/health/coronavirus-unveiled.html

Goal: Use the laws of physics to understand and predict molecular properties and interactions between molecules

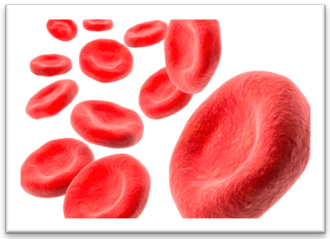
DIFFERENT RULES AT DIFFERENT LENGTH SCALES

Theory

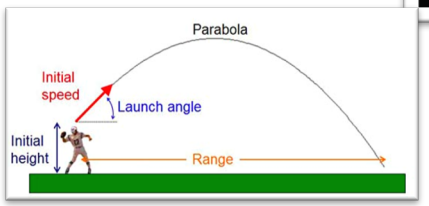
Relativity
$\sim 10^{21}$m



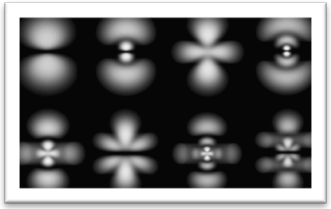
Classical Mechanics
10^{-9} m



Classical Mechanics
10^{-6} m



Classical Mechanics
1 m



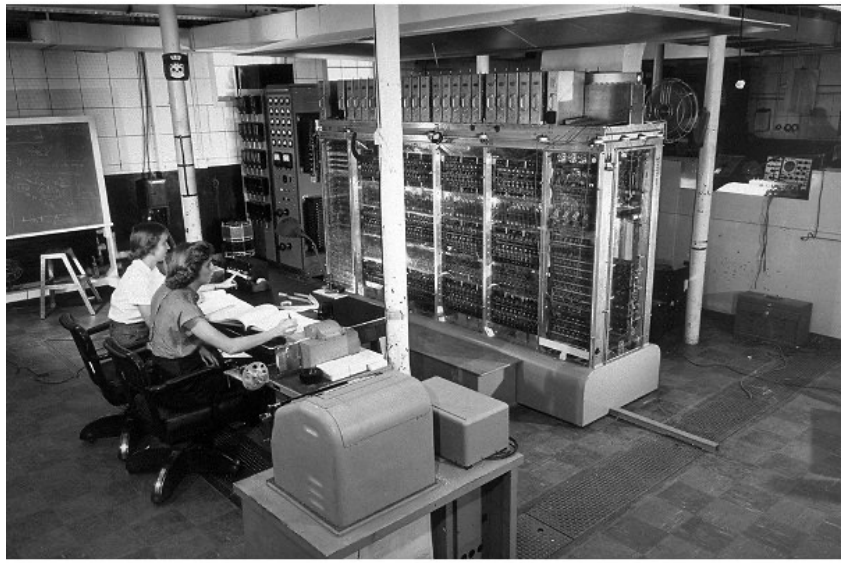
Quantum Mechanics
10^{-12} m

Particle Physics
10^{-18} m

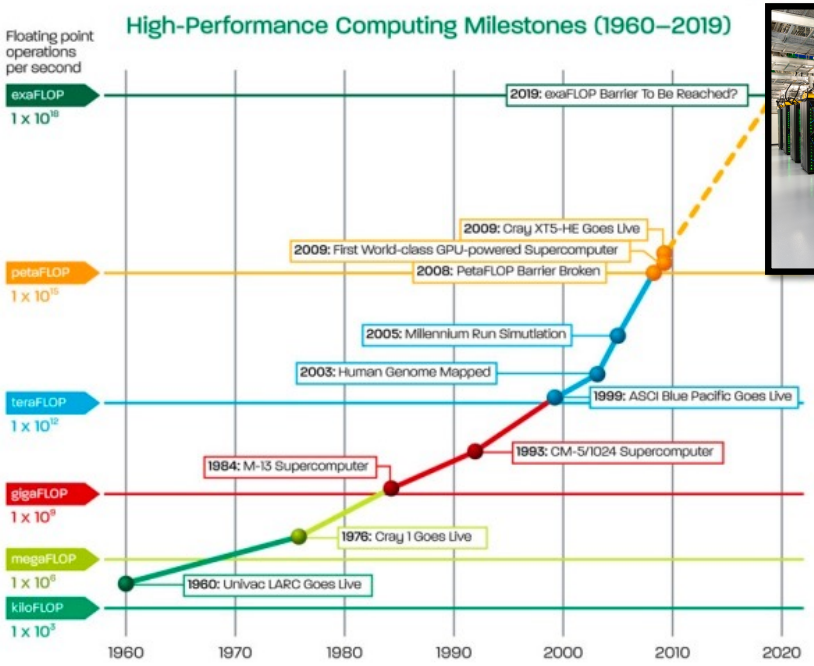
Size/Mass

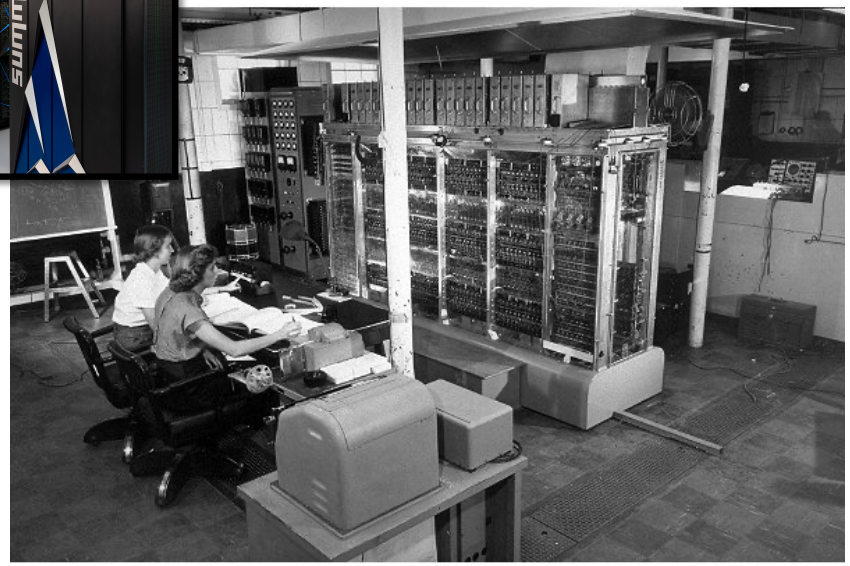
NEED FOR COMPUTERS

- Equations are too complicated to solve by a person in most cases
- Used to make the most approximation that seemed reasonable, then sometimes use computers as calculators
- Computers first applied in chemistry during the Manhattan Project to predict nuclear properties



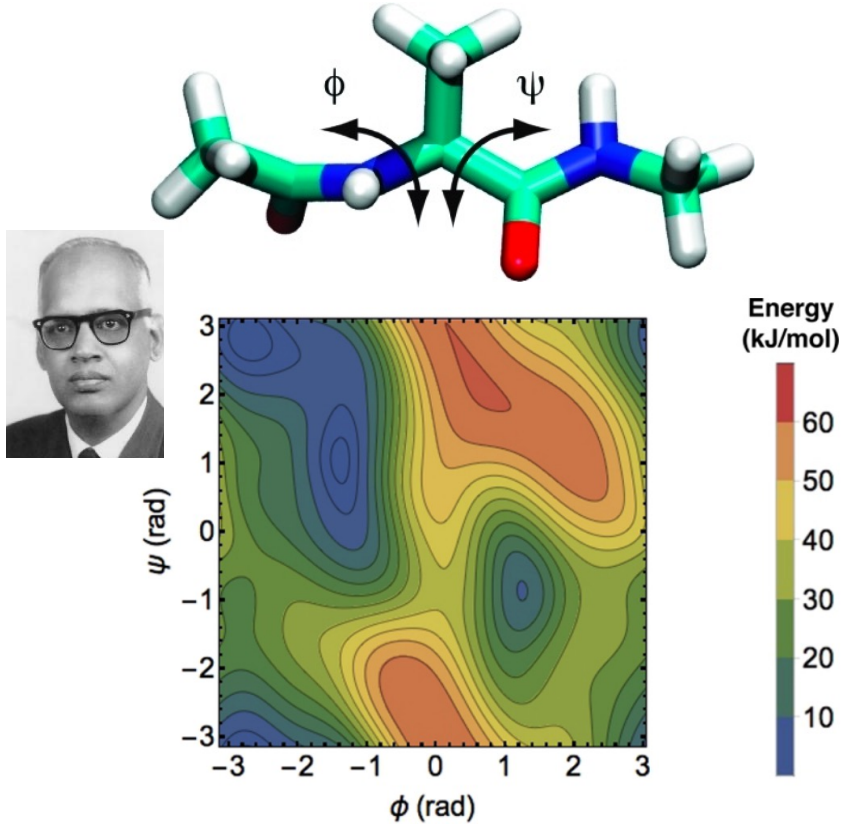
ADVANCES IN COMPUTING POWER





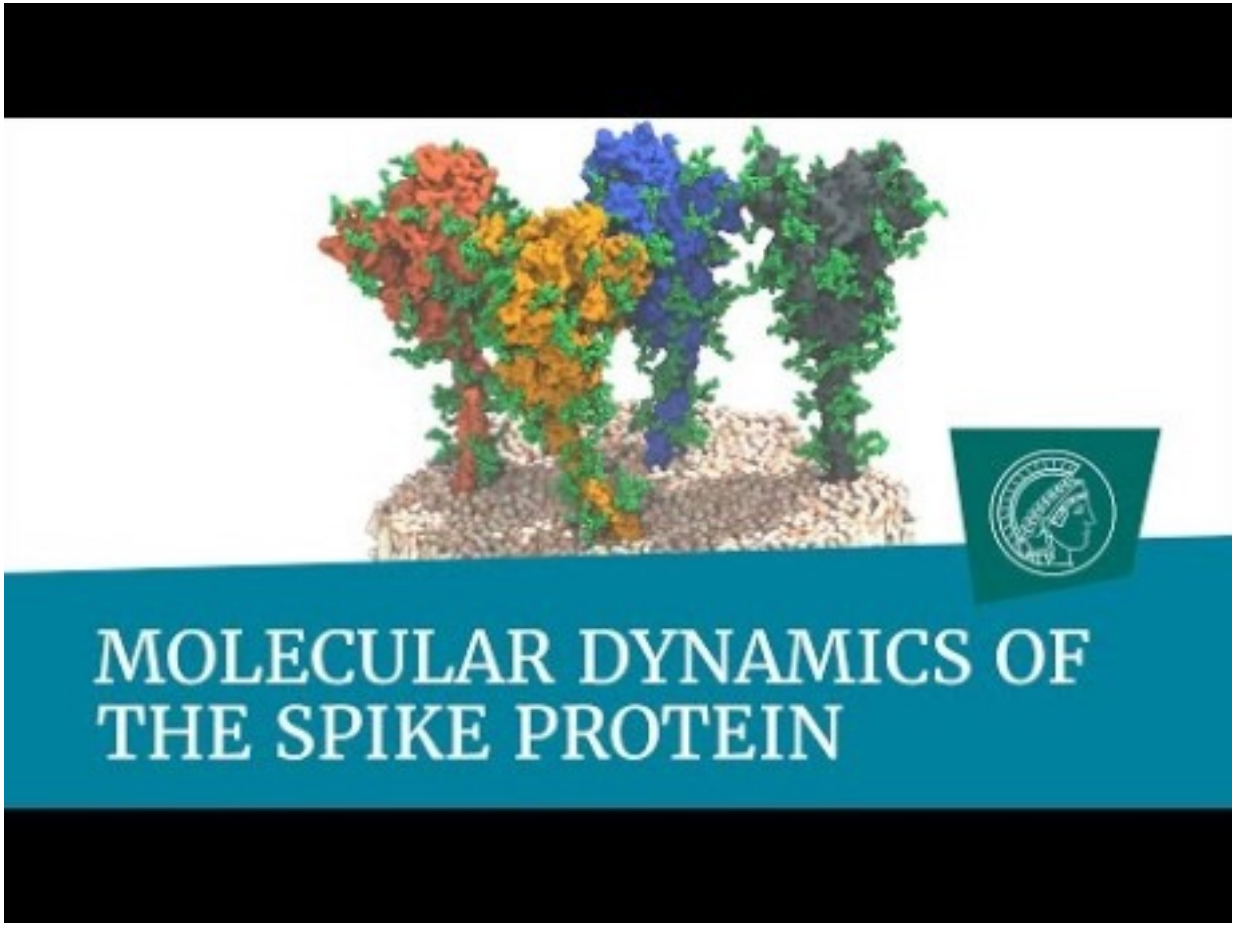
Molecular Dynamics Simulations

- **Simple idea:**
  F = m a → positions, velocities of atoms
  - Where do forces come from?
- Molecular mechanics "forcefield" built to reproduce experimental and quantum mechanical data
  - Atoms
    - Mass
    - Charge
    - Excluded volume
    - van der Waal's interactions
  - Bonds
    - Stretch
    - Bend
  - Torsion



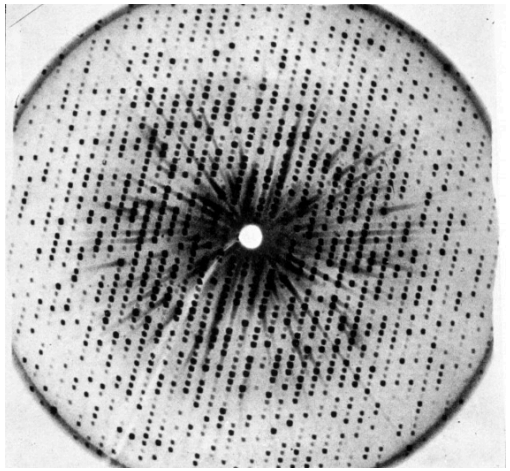
Need a starting structure!

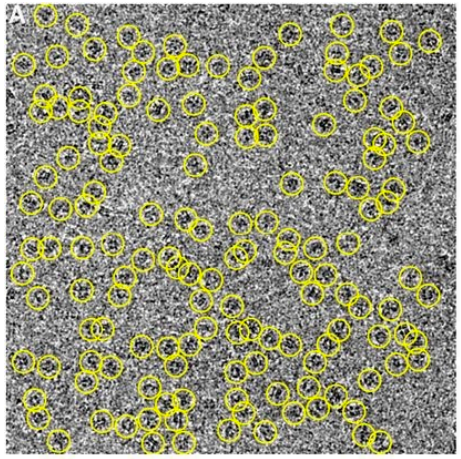
EXAMPLE SIMULATION FROM SARS-COV-2 PROTEIN

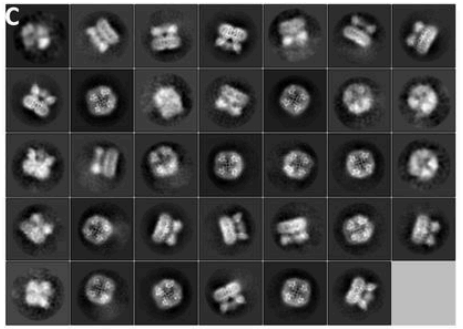


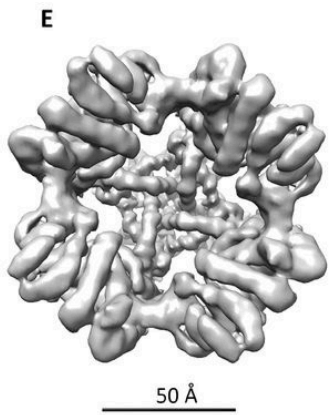
How to get a starting structure

- In order to simulate a protein, we need a good guess of the starting structure
- When we see things, it is because visible light bounces off something and goes in our eye (light detector)
- In order to see how the atoms are arranged in a molecule, we need to bounce something off of them which are shorter than the distance between them: X-rays (wavelength ~0.01 to 10 nm) or electrons (much smaller)

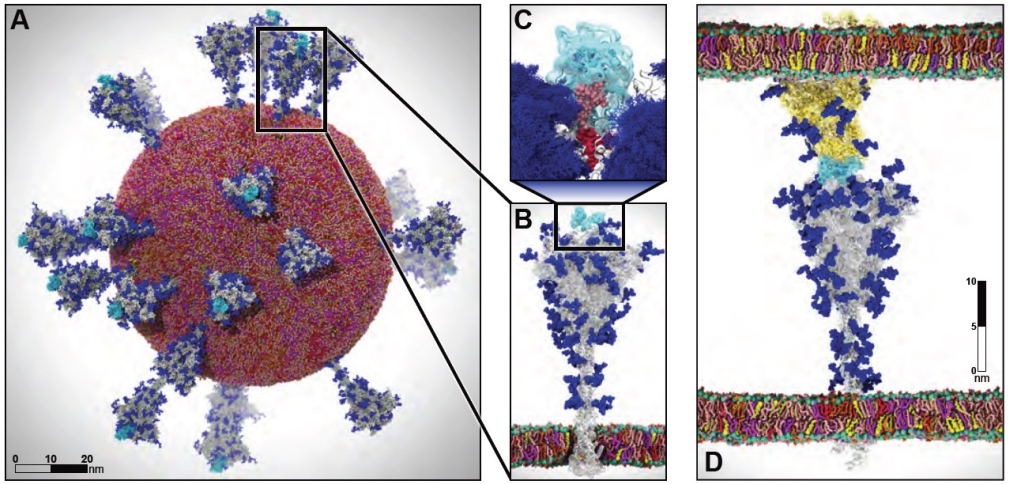




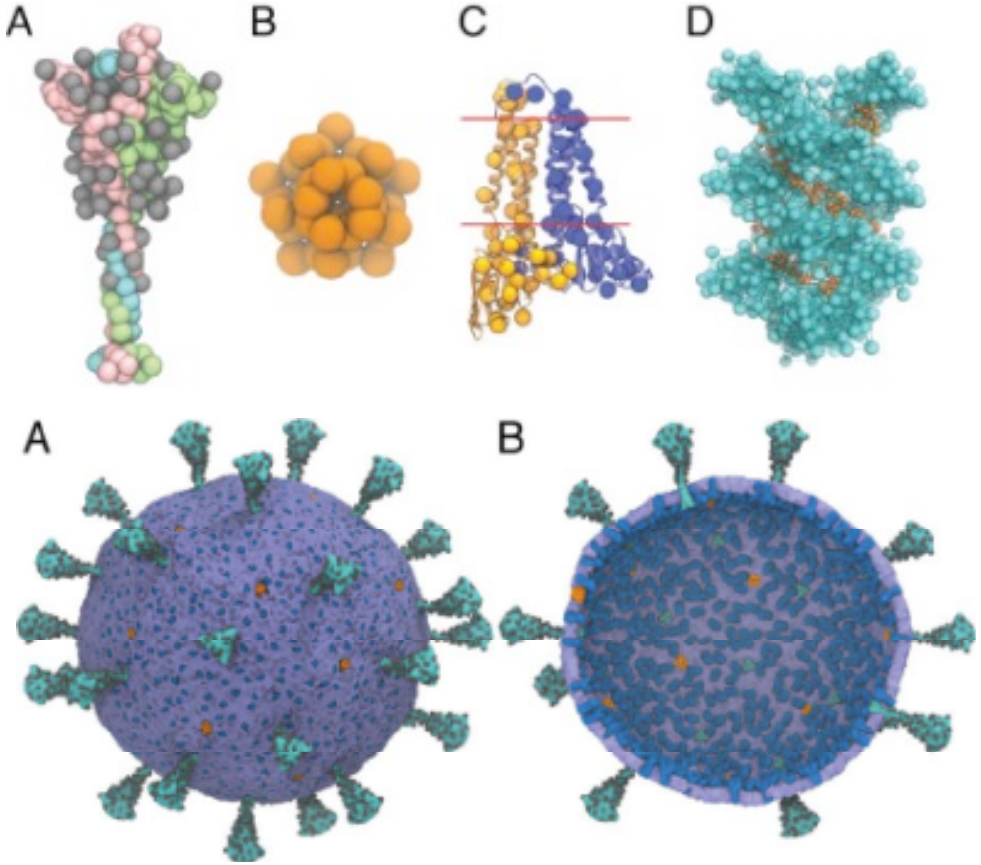




SIMULATING THE "WHOLE VIRUS"



305 Million atoms on Summit supercomputer – up to 50 ns/day
Casalino…Amaro, Supercomputing '20



Yu, …, Amaro, Voth. bioRxiv 2020.10.02.323915

WHAT'S THE POINT?

1) Computers can make a prediction of how proteins interact with each other or with drug molecules
2) In the computer, we can quickly change the protein to see what the effect of a mutation (virus variant) might be
3) These can be used to guide the direction of new experiments and help provide intuition at a molecular level