Computer simulations to study SARS-Cov-2 proteins

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“...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 jiggling and wiggling of atoms.”

– Feynman Lectures in Physics, 1964

“...all things are made of atoms” = Chemistry
“...jiggings and wigglings” = Physics
Goal: Use the laws of physics to understand and predict molecular properties and interactions between molecules
Different rules at different length scales

- **Relativity**
  - ~$10^{21}$ m

- **Classical Mechanics**
  - $10^{-9}$ m
  - $10^{-6}$ m
  - $10^{-9}$ m

- **Quantum Mechanics**
  - $10^{-12}$ m

- **Particle Physics**
  - $10^{-18}$ m
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
• **Simple idea:**
  
  \[ F = ma \rightarrow \text{positions, velocities of atoms} \]

  • 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

MOLECULAR DYNAMICS OF THE SPIKE 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
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.