

**Source:**

## 1 | Preliminary Research

### 1.1 | Sources

<https://www.frontiersin.org/articles/10.3389/fchem.2019.00540/full>

### 1.2 | Notes

#### 1.2.1 | Target Processes

1. Enzyme catalysis
  - catalyzing reactions with actions
2. Protein-ligand binding
  - neurotransmitters (dopamine), protein is dopamine receptor how does the ligand bind the proper site to open the channel?
    - ligand: how to pronounce?
3. signal transduction
  - bind to other protein to trigger chain of actions
    - release calcium from intercellular stores
4. allosteric regulation
  - a reason why knowing the structure and pockets is important
  - predict allosteric sites
    - similar to non-competitive inhibition?
    - but for dna binding proteins, like the dna transcription inhibitor
  - ligand binds allosteric site and activates the protein

#### 1.2.2 | Folding Simulation Methods

1. all-atom molecular dynamics (MD)
  - Obtains all desired information regarding the kinetics and thermodynamics
- (a) Time scale bottleneck
  - very slow (supercomputers -> microseconds of simulation)
  - require microsecond to millisecond time scales
- i. optimizations
  - A. conformational sampling?
    - retains atomistic representation of the system
  - B. overcome kinetic trapping and thorough sampling of conformational space techniques
    - umbrella sampling
    - multicanonical algorithms
    - simulated tempering

- transition path sampling
- targeted molecular dynamics
- replica exchange method molecular dynamics (REMD)
- accelerated molecular dynamics (AMD)
- see below

## 2. Accelerated molecular dynamics (AMD)

epic

### 1.2.3 | **Voltage gated ion channels**

#### 1. overview

- (a) lives on cell membrane
- (b) role
  - i. allows ions in/out
  - ii. crucial in "excitable" cells, like neurons
  - iii. propagates electrical signals directionally
  - iv. ion specific
    - A.  $\text{Na}^+$
    - B.  $\text{K}^+$
    - C.  $\text{Ca}^{2+}$
    - D.  $\text{Cl}^-$
  - v. triggered by voltage across cell membrane
- (c) parts
  - i. voltage sensor
  - ii. pore/conducting pathway
  - iii. gate

### 1.3 | **Meetings**

#### 1.3.1 | **12 oct 2020**

- computational prediction modeling
  - trying to predict the crystal structure
    - why?
      - to analyze would this fit?
      - does it work with this target
- solving the structure
  - xray crystallography
    - gold standard
    - now got the structure
      - what does that mean?
      - can we simulate how it interacts?
      - can you then do modeling on that to see if drug molecules work? are useful
- look at some concrete examples?
- tell a biological story alongside with computational relevance piece

## 1. protein synthase

not as much simulation stuff

## 2. neurotransmitters

dopamine sodium rushes in, electrochemical and concentration gradient recharge gradient by releasing potassium

## (a) nerst equation

electrochemical gradient as battery

## (b) goldman-katz equation

- applied to neuro
- takes into account the concentrations of the 4 ions
  - how does the power of the battery work given those components?
  - ligands and pH can change/denature proteins, but there are also voltage gated channels

## 3. Voltage Driven Things

- Heartbeat
- nervous system
  - how do voltage gated ion channels work?

## (a) things to know about

- action potential
- voltage gated calcium channels open at depolarization threshold

## i. neurotransmitters

- "calcium mediated exocytosis of neurotransmitter vesicles in the synaptic terminal"
- calcium rushes somewhere to allow the neurotransmitters to leave the cell

## 4. Case study

- why do we care? why is this useful
- knowing the structure can lead to some useful information
- how did it lead to some sort of accelerated understanding?

## 5. prions

- how to pronounce?

## (a) CJD

- is it inheritable?
- one case per million population

## i. Cases

- the gene that causes CJD in 5-10% of cases is PRNP
- 87% of cases are sporadic

## (b) isoform

- a different set of introns and exons
- spliceosome takes pre-RNA and cuts out introns
  - even if the pre-RNA had 10 exons, the spliceosome might take a subset of those exons and remove the others
- An isoform is a variant of that subset, an abnormal isoform is one that is "bad" and causes problems