

# Computationally Predicting and Characterizing the Immune Response to Viral Infections



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# COVID-19 Disease Severity

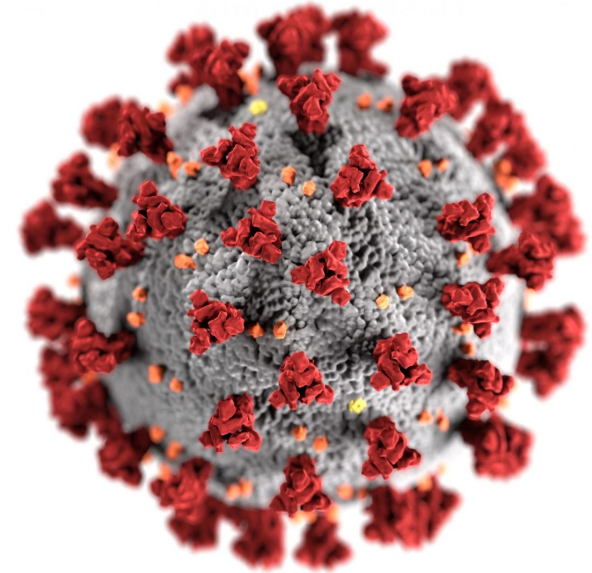
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Of those who contract SARS-Cov-2, approximately:

- 33% show **no** symptoms
- 48% show **mild** symptoms
- 14% show **severe** symptoms
- 4% show **critical** symptoms
- 1% **die**

Factors influencing disease severity:

- Age, sex, comorbidities.
- Past exposure to similar viruses.
- Innate differences in an individual's immune system.



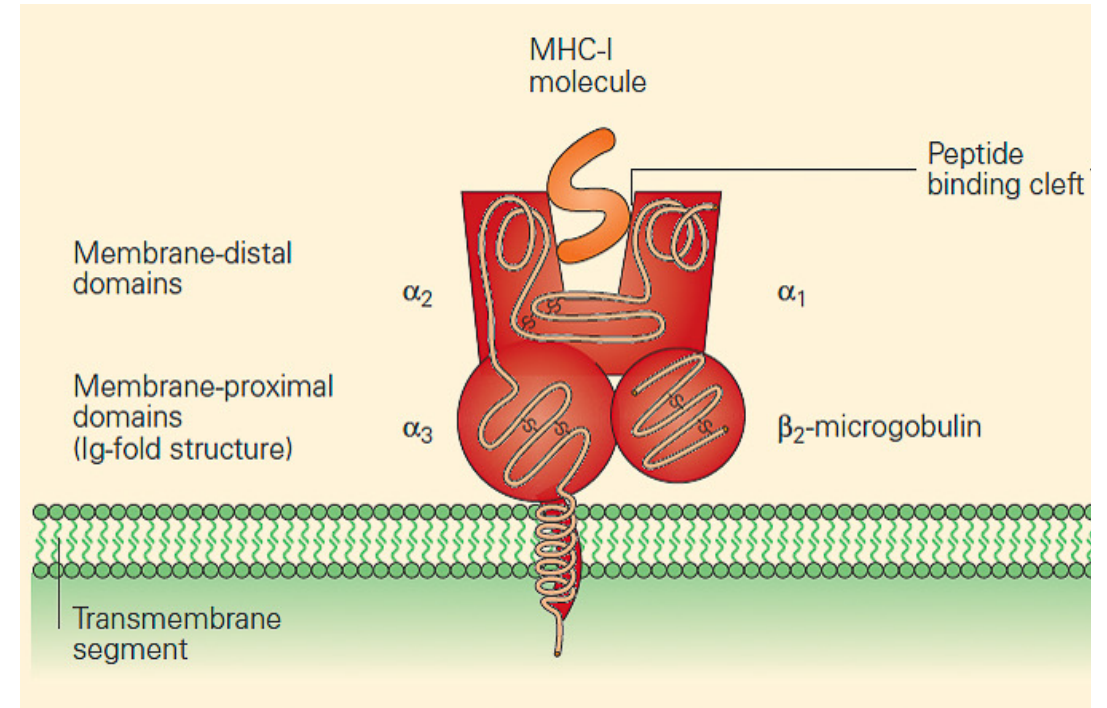
*Our topic of study:*

Computational prediction of cellular response to pathogens, at molecular scale.

# Cellular Immune Response

*First line of defense against viral infections (and cancer), present in all nucleated cells in body.*

- Foreign proteins in cells are cleaved into smaller fragments (called **peptides**).
- These are transported to the cell surface.
- There they can bind to receptor molecules called **MHC Class I** molecules.
- Once bound, these become targets for the immune system:  
**killer T-cells** will come and kill off the infected (or cancerous) cells.



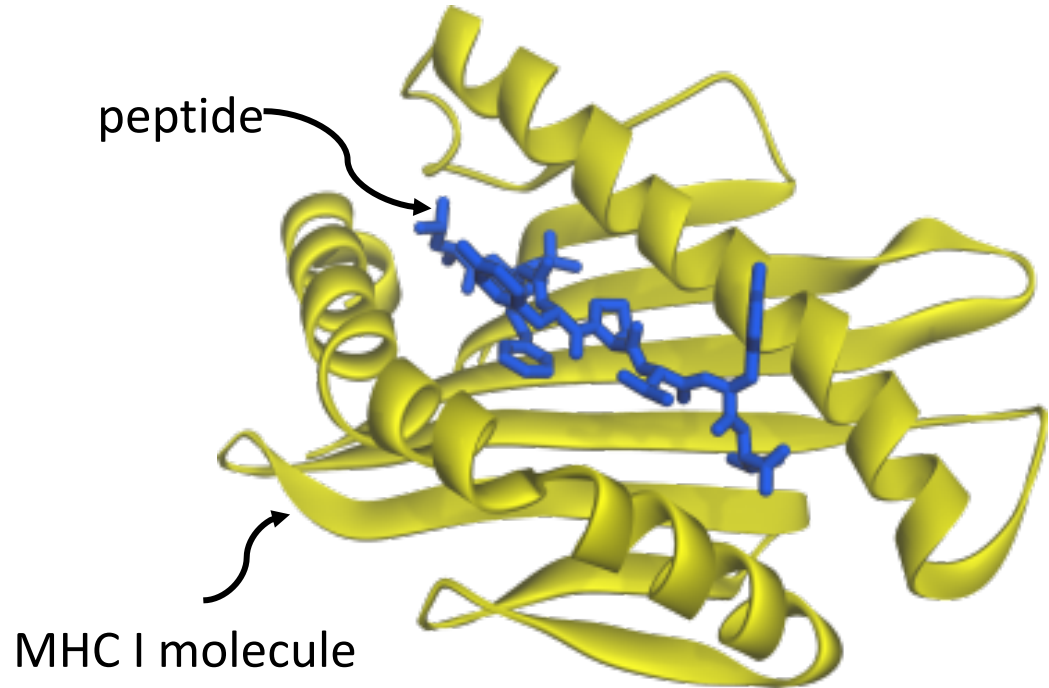
*If effective, this cellular response means individual likely will show only mild symptoms.*

*If not, infected cells become factories for the virus, and individual will have full-blown infection.*

# Understanding Cellular Immune Response

Critical for:

- Understanding and predicting disease severity for a **novel virus**.
- **Vaccine** development.
- Understanding and predicting impacts of viral **mutations**.
- **Cancer** immunotherapy.
- Understanding **auto-immune** diseases.



Individual has up to **6 different** MHC I molecules.

Diversity: **21,000 variants** in human population.

Core problem:

*Predict whether peptides associated with virus will bind to an individual's MHC I molecules.*

# Prior Work: Predicting MHC Peptide Binding

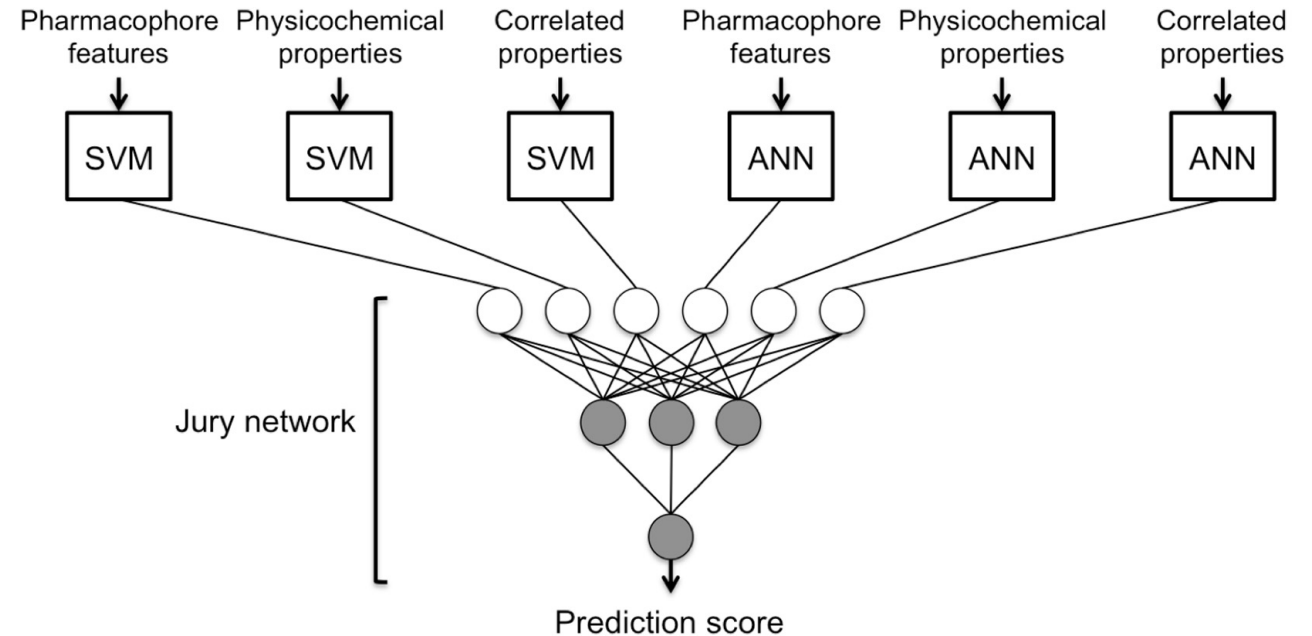
## Experimental:

- Crystallography, elution, mass spectroscopy, etc.

## Machine Learning & Neural Networks:

### NetMHC

- Training data: binding strength for known MHC I/peptide pairs.
- Given new peptide, inference based on similarity of amino acid sequence.



MCH I label

HLA-A\*02:1010:01:02N

Peptide Sequence

ACTTTWYCGH

Strength

36

Limitation:

*Spurious inferences*

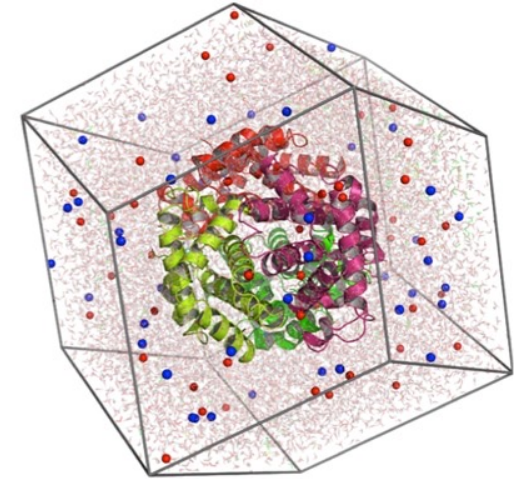
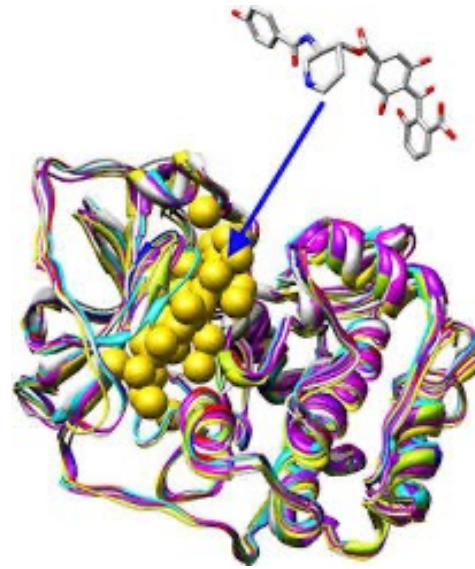


# Prior Work: Molecular-Level Simulation

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Variety of general-purpose techniques:

- Molecular Dynamics
- Monte Carlo
- Simulated Annealing
- Molecular Docking



*Limitation:*

*In principle accurate, but all techniques are computationally intensive.*

*Hours (or days) of computing time per peptide/MHC molecule pair.*

*Scale: ~1 billion combinations.*

*~38,000 peptides for SARS-Cov-2*

*~21,000 MHC I variants*

# Our Approach

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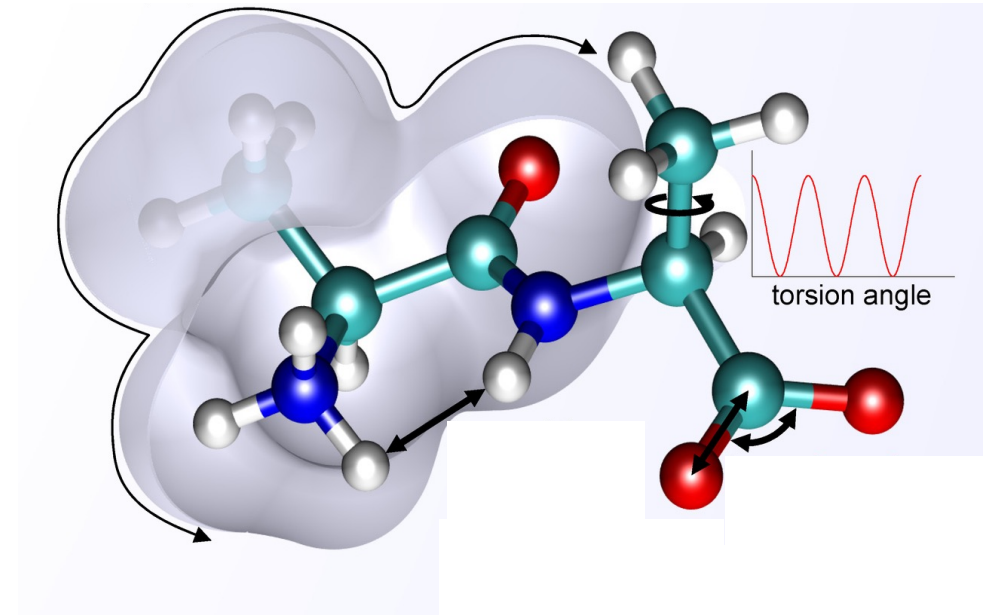
## Simulate Molecular Mechanics

### Highly Targeted:

- Start with peptide, *correctly aligned*, inside cleft of MHC molecule.
- Perform moves in *torsional space* to find optimal configuration

### Deploy at scale:

- Develop **parallel** algorithms for GPUs.
- Deploy on **cloud-computing** infrastructure.



Turns 1 billion days of computing time to 1 million minutes of cloud-computing time.

# Challenges: Simulating Molecular Mechanics

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Must infer structure:

- For SARS-Cov-2 (and nearly every emerging pathogen), peptide sequences is ewn, so **~38,000** brand new peptides.
- Of **~21,000** MHC I variants, only ~200 structures known from crystallography. *Most know variants are from Western Caucasian demographic.*



Will **infer** structure starting with similar peptide/MHC complexes and substituting amino acids that differ. *Refold and fit peptide into cleft in one step.*



# Impact

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Can easily determine specific variants of MHC I molecules for an individual through [HLA typing](#).

Predict:

- Disease severity for a new pathogen for *different* individuals.
- Disease severity for *different variants* of a virus for *different* individuals.
- Effectiveness of *different* vaccines for *different* variants of a virus for *different* individuals.

Also:

- Characterize good targets for cancer immunotherapy.
- Characterize good targets for auto-immune disease treatment.