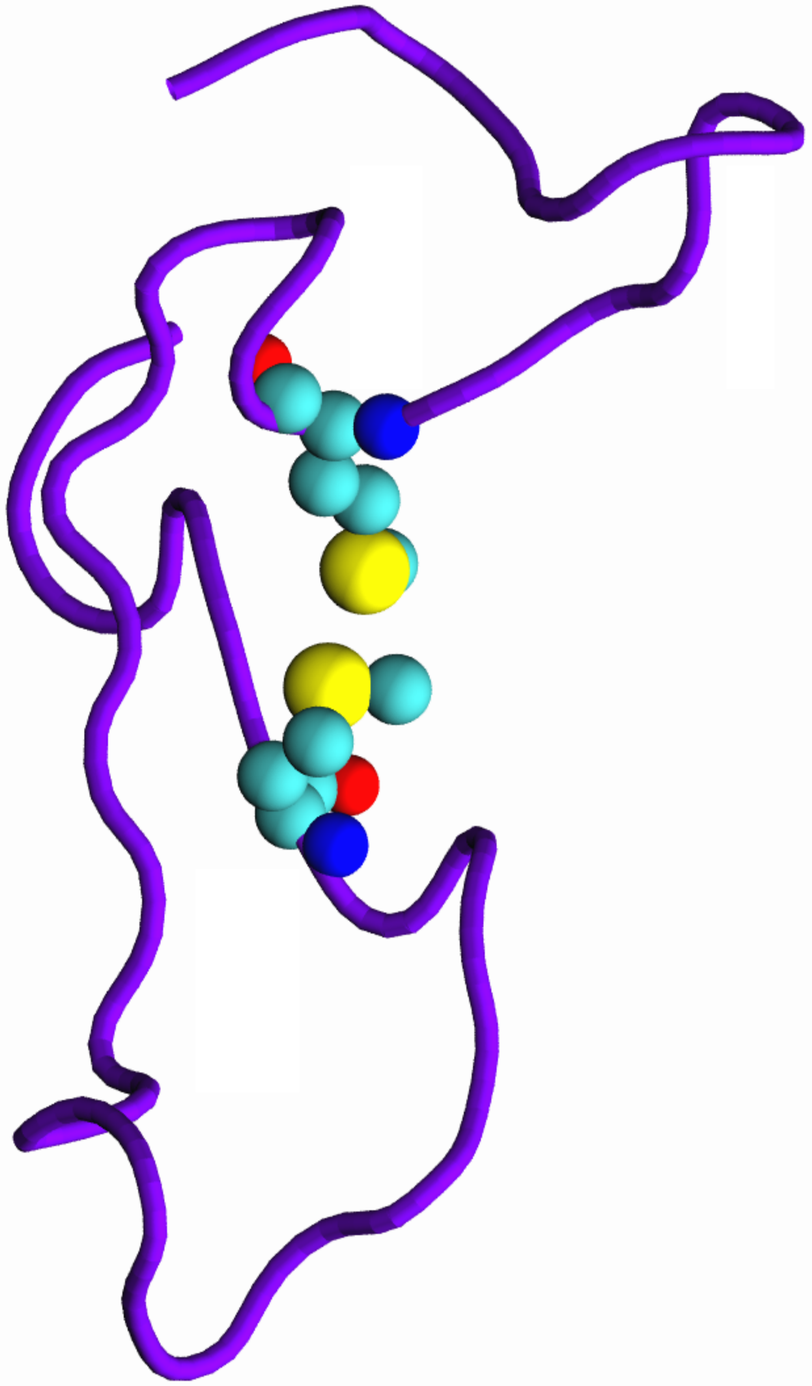
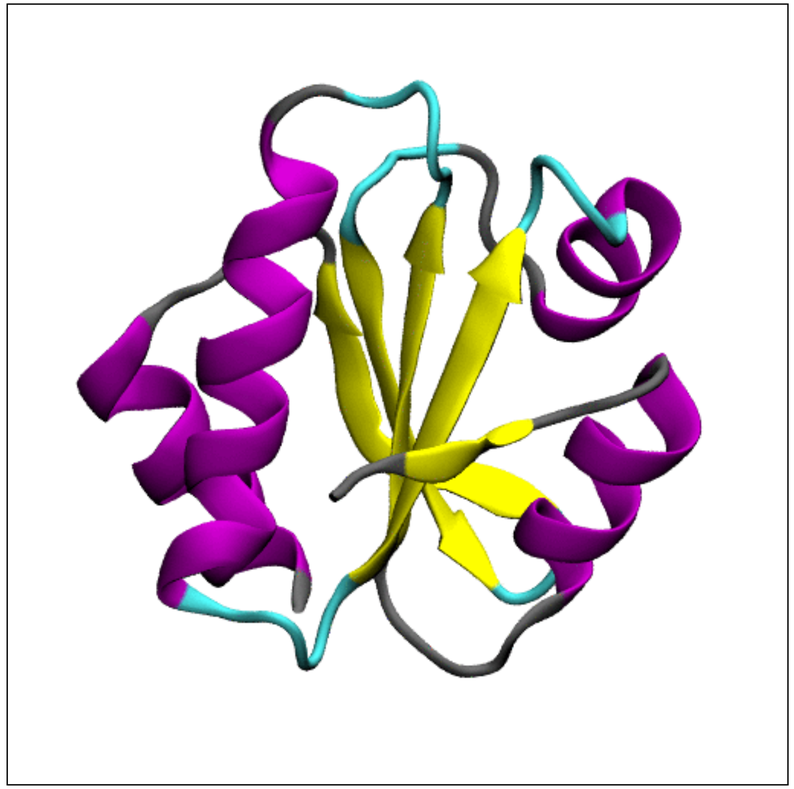
# The Role of Methionine-Methionine Interactions in the Conformations of Intrinsically Disordered Proteins

Connor Pitman - November 9th 2021



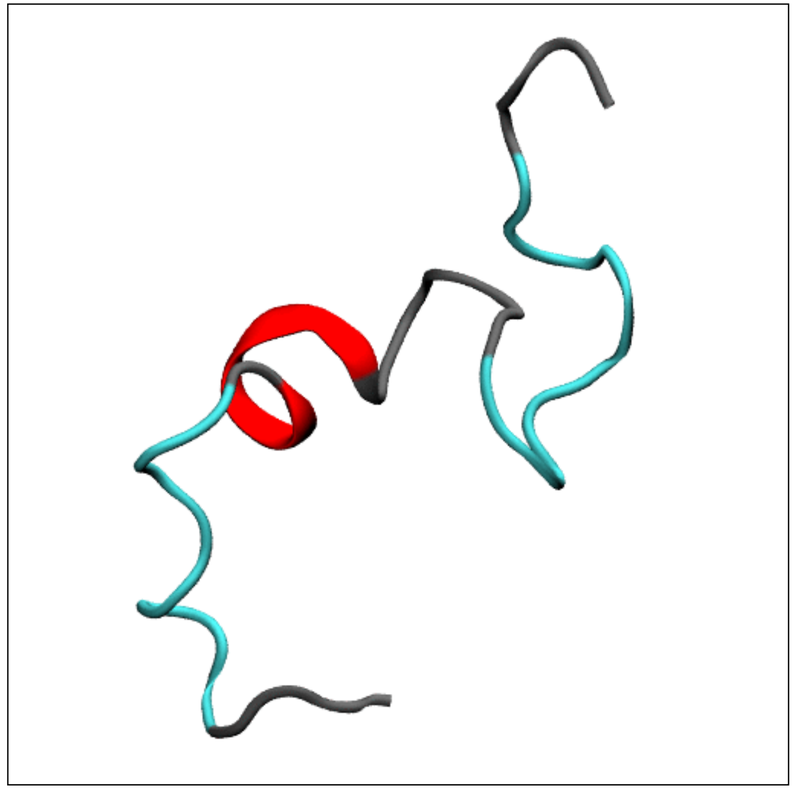
# Intrinsically disordered proteins lack a well-defined structure

**Structured**



yeast Thioredoxin

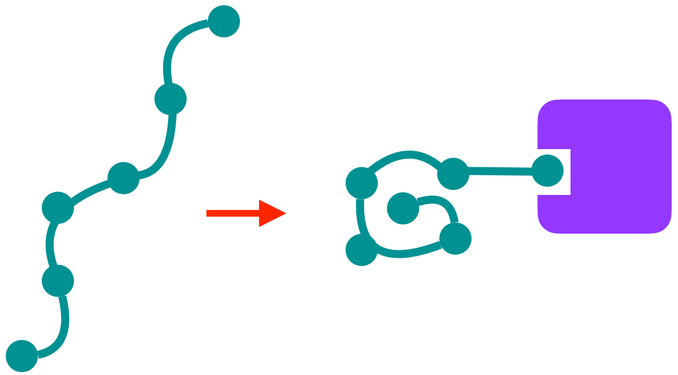
**IDPs**



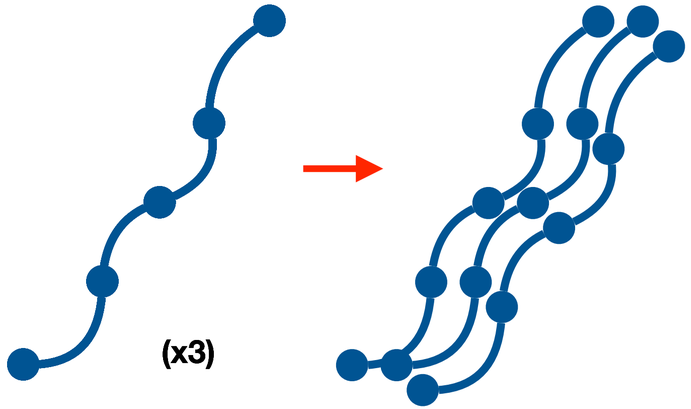
BDNF prodomain

Movies courtesy of Dr. Ruchi Lohia

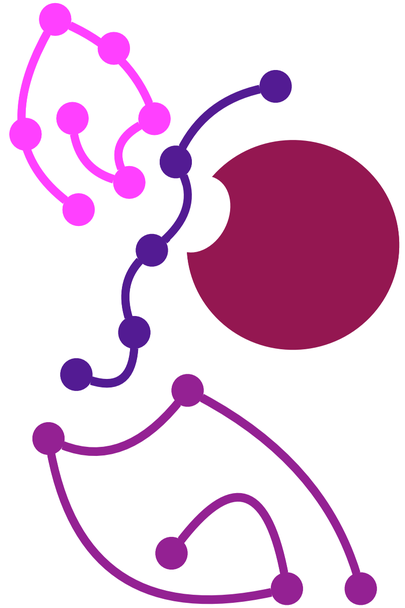
# The Many Roles of Intrinsically Disordered Proteins



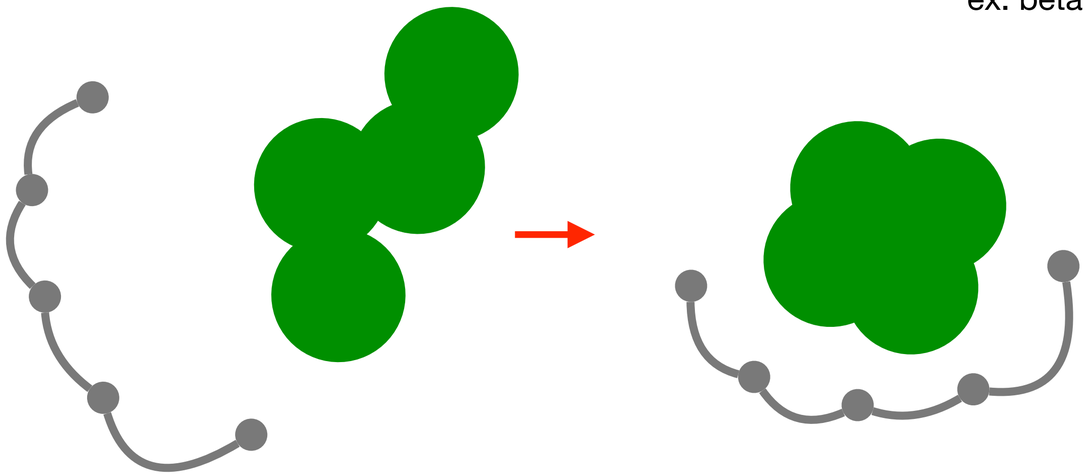
Signals
ex. BDNF prodomain




Aggregates
ex. beta amyloid



Interaction with multiple binding partners
ex. calmodulin, p21, p53



Chaperones
ex. Hsp-33

# Sequence, function, and IDPs

- Mutations to IDPs have functional consequences
- Examples:
  - BDNF prodomain → Neurodegeneration
  - MeCP2 → Rett's syndrome
  - p53 → Cancer
- Mutations in IDPs can still produce phenotypic effects

# *in vitro* or *in silico?*

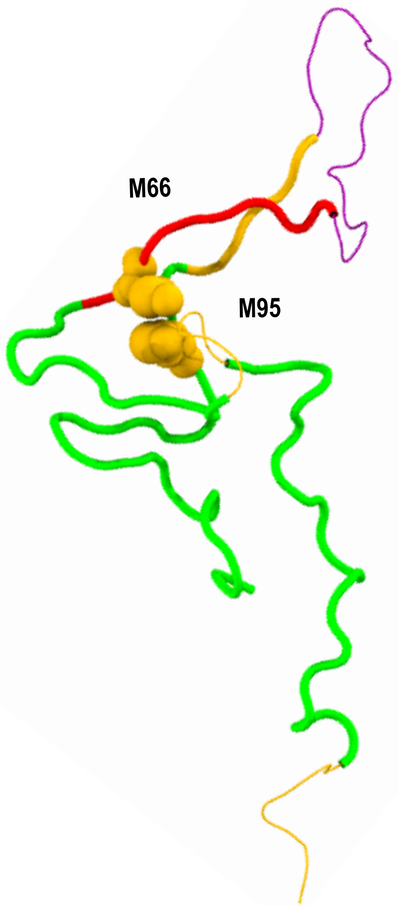
## Experimental Methods

- NMR, Cryo-EM, x-ray crystallography, etc.
- Great for proteins that fold into a well-defined structure
- Great for resolving a single stable structure
- IDPs by nature don’t form tertiary structures. They explore many relatively unstable structures

## Computational Methods

- Molecular Dynamics Simulation
- Allows the protein to sample many possible conformations
- Can use computational tools to analyze the protein as it moves
- Drawback - long time to run, computationally expensive

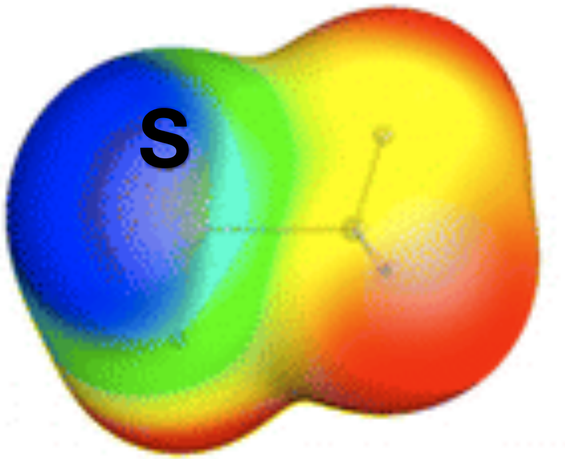
# The Brain Derived Neurotrophic Factor Prodomain

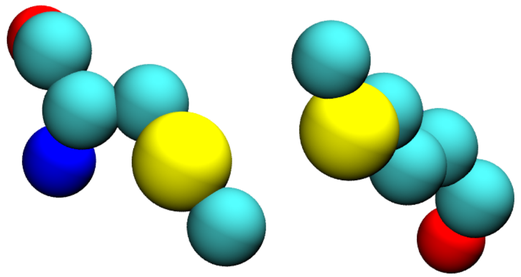



- Previous study done by our lab on another IDP
- BDNF prodomain
- Computationally expensive
- Total of 250 μs worth of data
- Study looking into the mechanism behind conformational changes caused by the Val66Met mutation
- Identified a significant role for Met-Met interactions
- Met-Met interactions hadn’t previously been considered in IDPs

# Methionine and… Methionine?

(1)



Two Methionines

- Methionine is one of two amino acids that contain sulfur
- This sulfur is highly polarizable
- Hydrophobic, but has special properties
- Favorable interactions identified in the crystal structures and quantum calculations (Gomez-Tamayo et al., 2016)

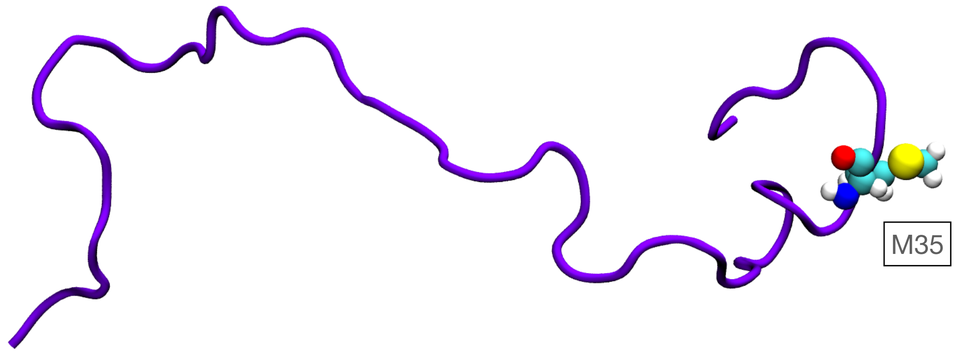
**1. Preferred Geometries and Energies of Sulfur–Sulfur Interactions in Crystal Structures** Ivana S. Antonijević, Goran. V. Janjić, Miloš K. Milčić, and Snežana D. Zarić *Crystal Growth & Design* **2016** *16* (2), 632-639 DOI: 10.1021/acs.cgd.5b01058

# Research Question:

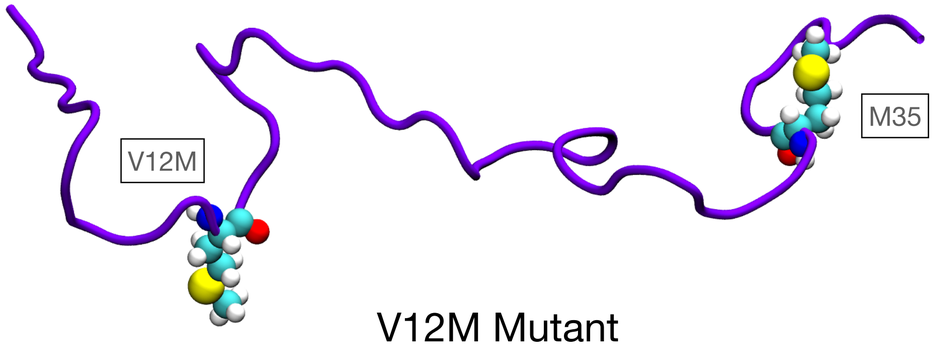
How do Met-Met interactions affect the conformations that an IDP can explore?

# Approach

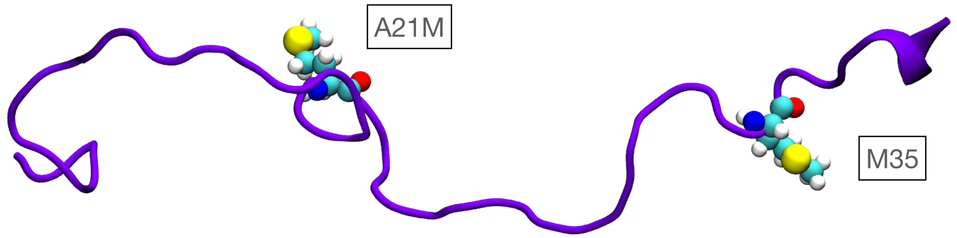
- Simulating the IDP Beta Amyloid
- Wild type peptide and two mutants
- Testing for changes in tertiary contacts between sections (“blobs”)
- Looking for specific Met-Met interactions using geometric parameters




Wild Type

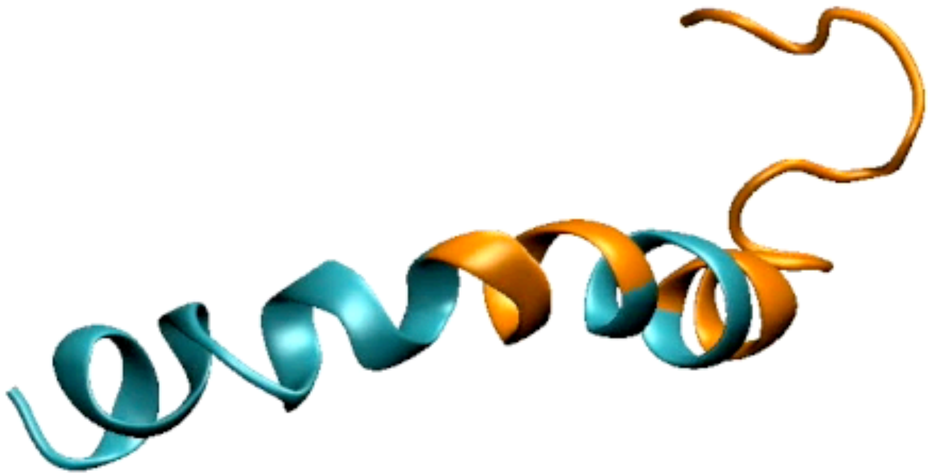



V12M Mutant



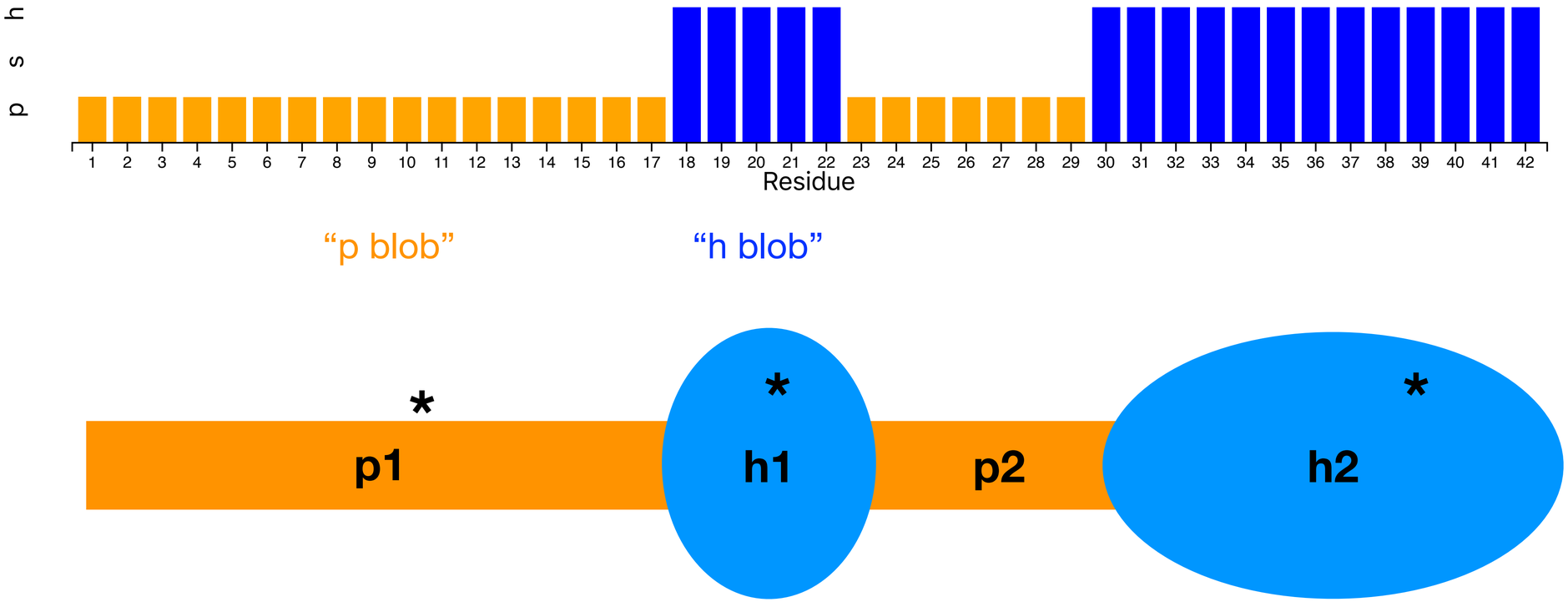

A21M Mutant

# Conformations from an MD simulation



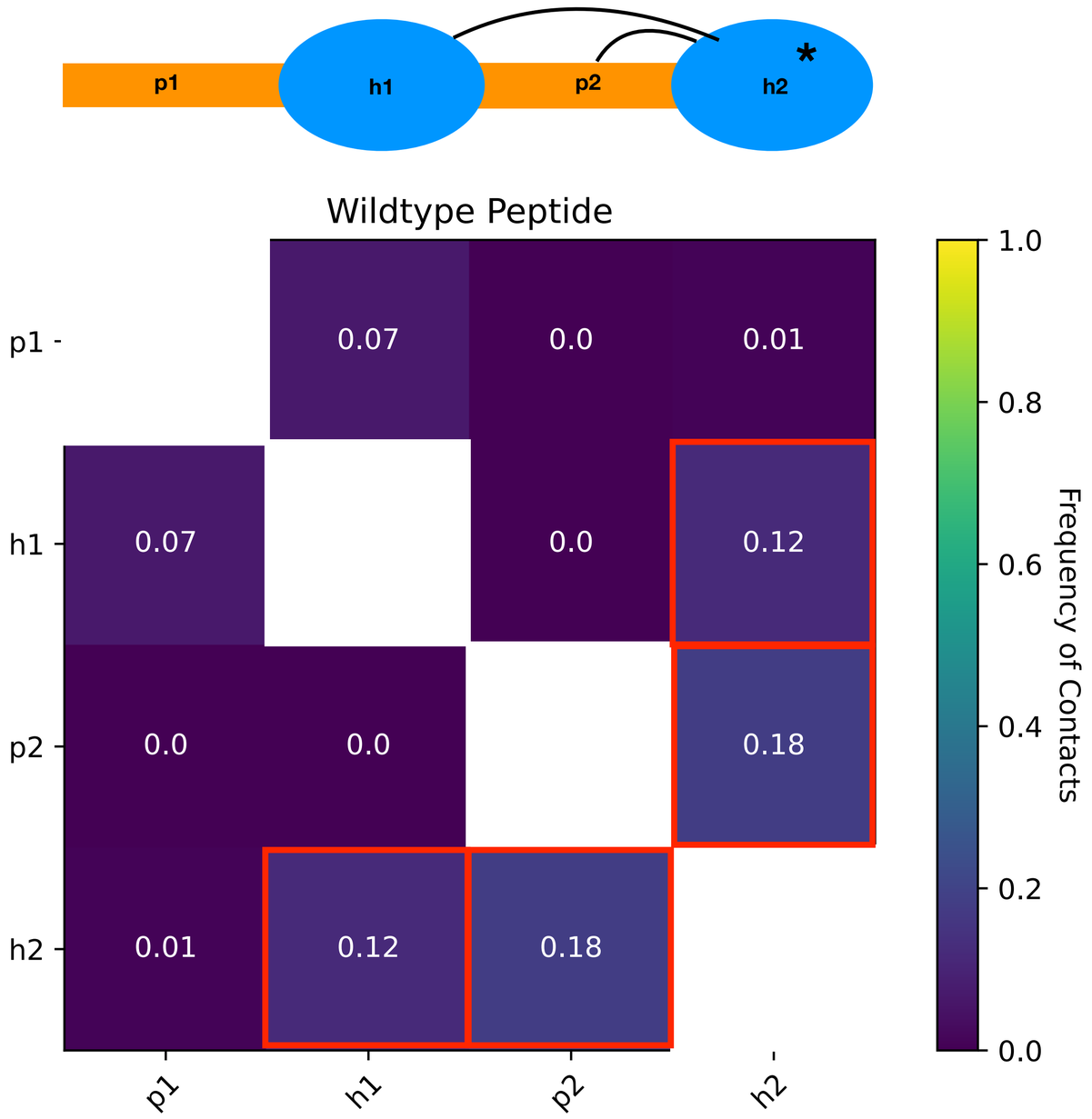
Wild Type
9.6 μs

# Defining segments of Beta Amyloid

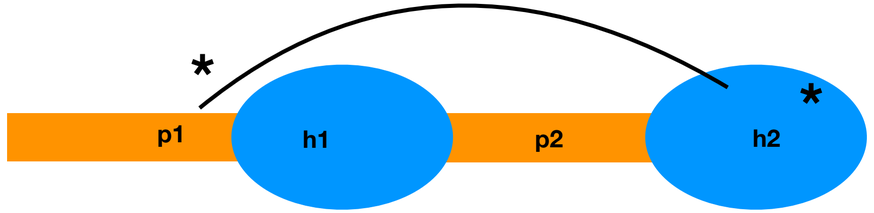


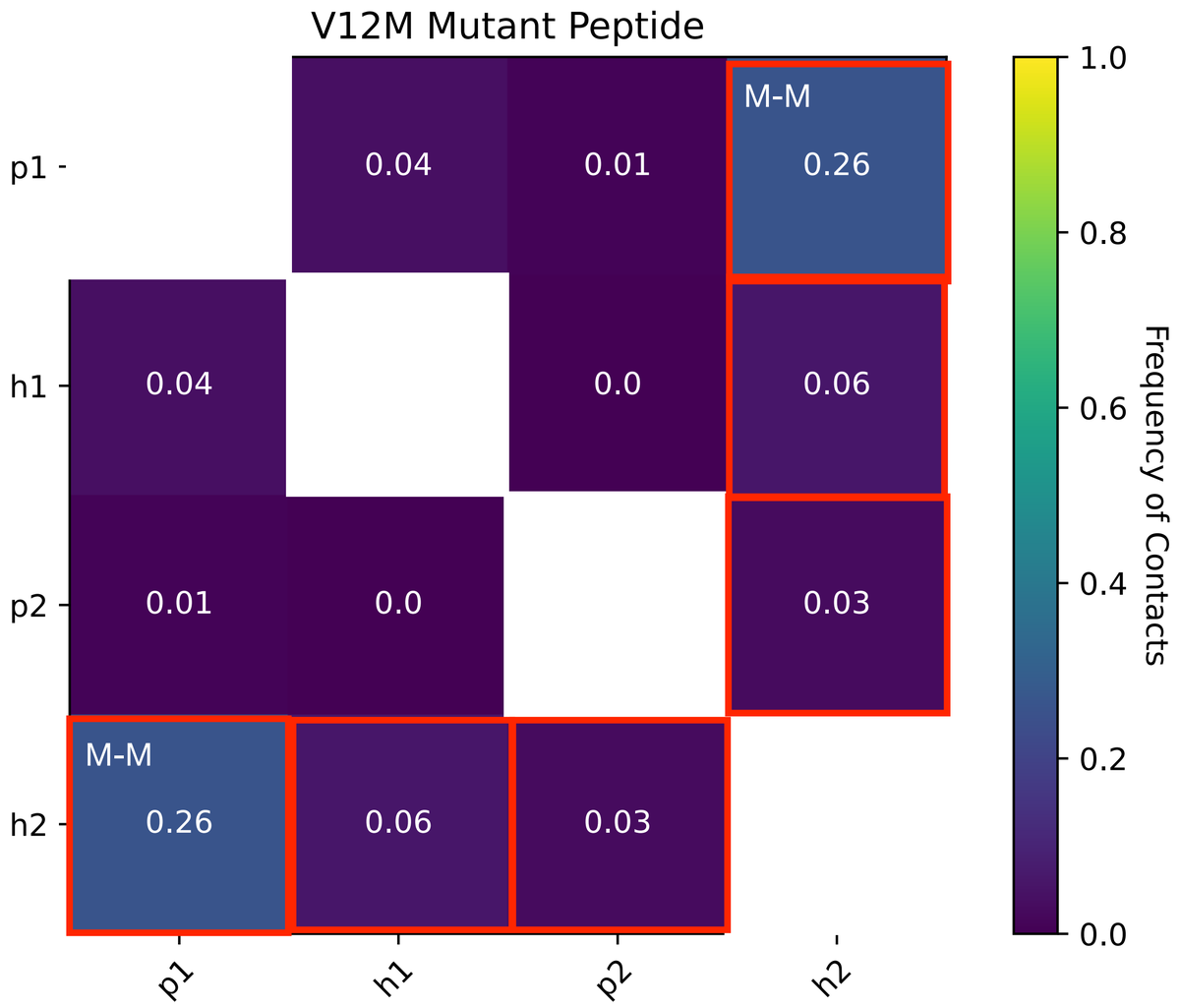

blobulator.branniganlab.org

# Measuring the frequency of blob contacts in the wildtype

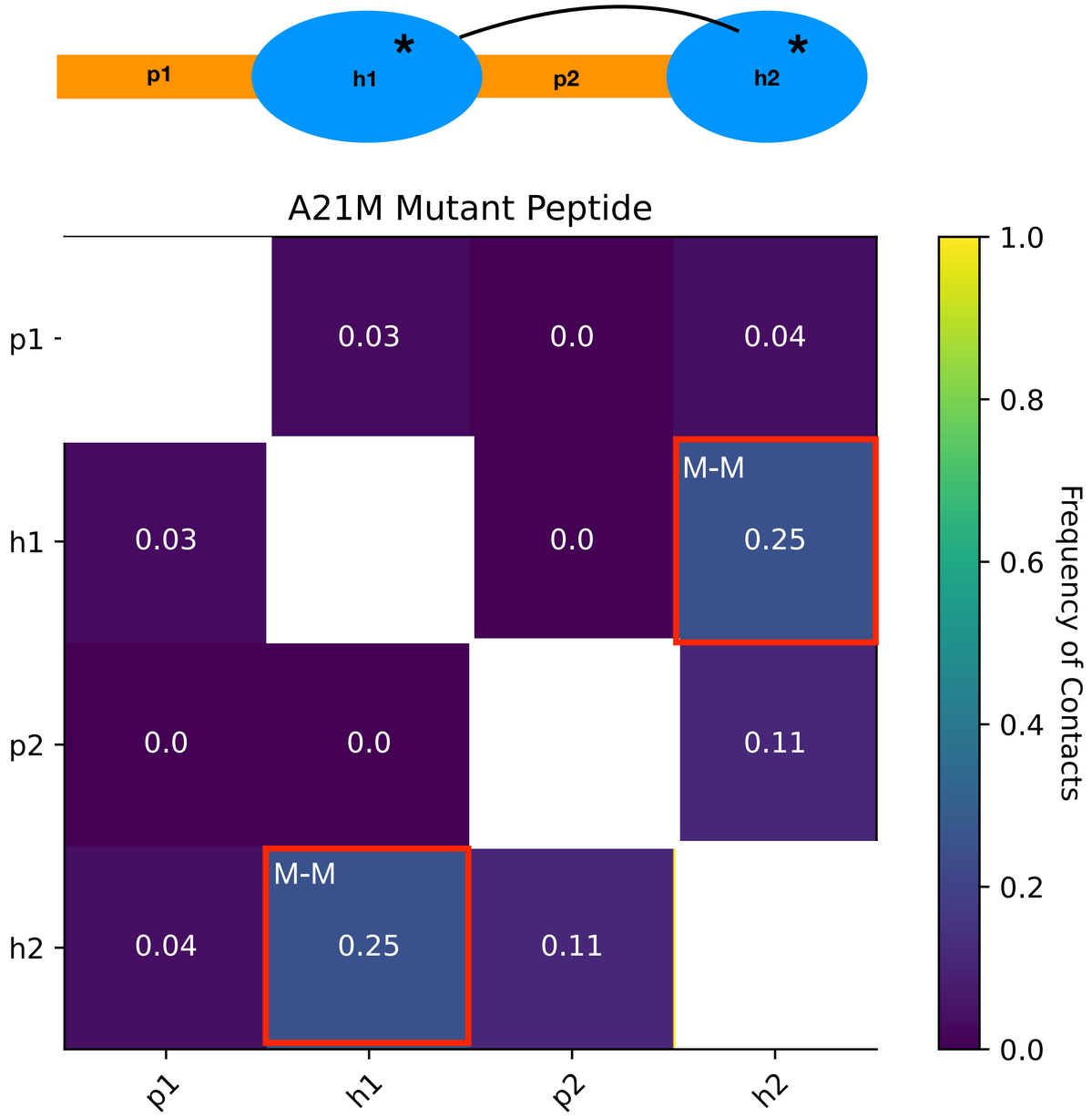


# Introducing the V12M mutation causes contact changes



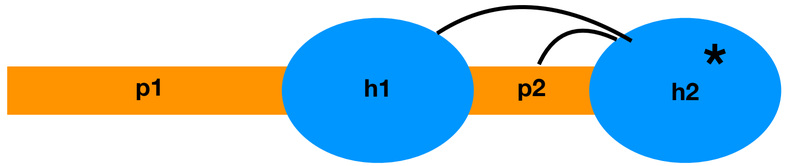



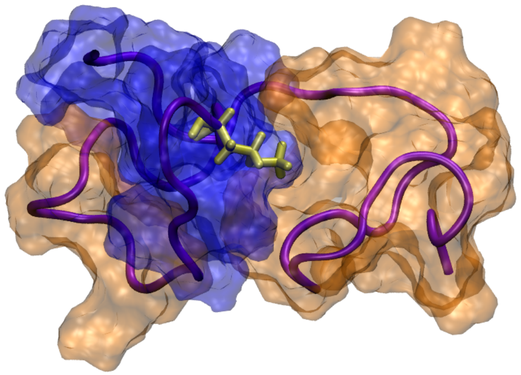
# Introducing the A21M mutation causes contact changes



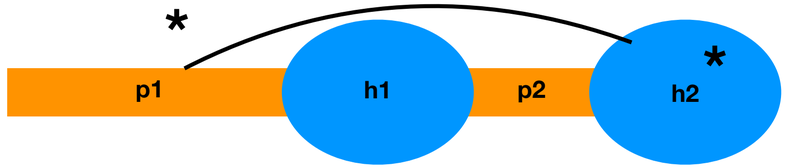
# Summary of Contact Changes

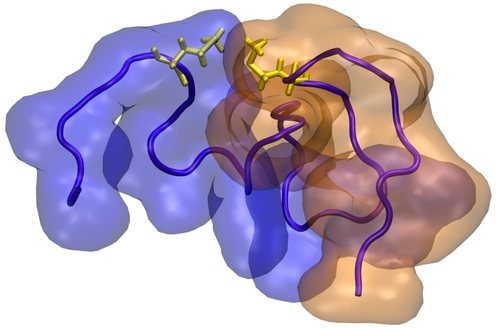
Wild Type



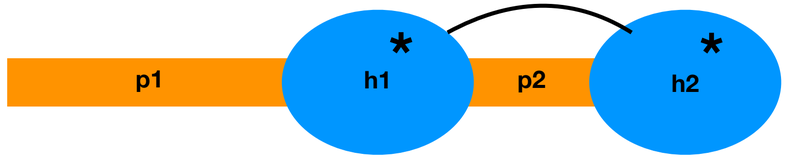



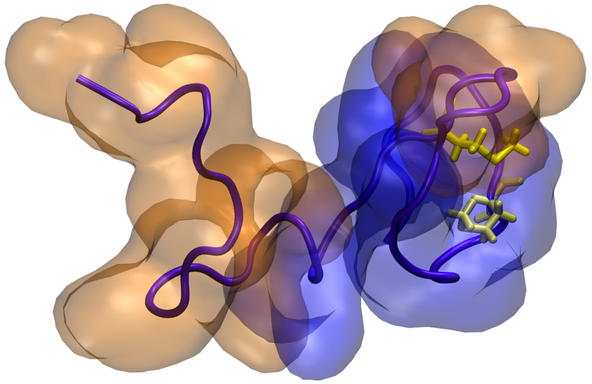
V12M Mutant



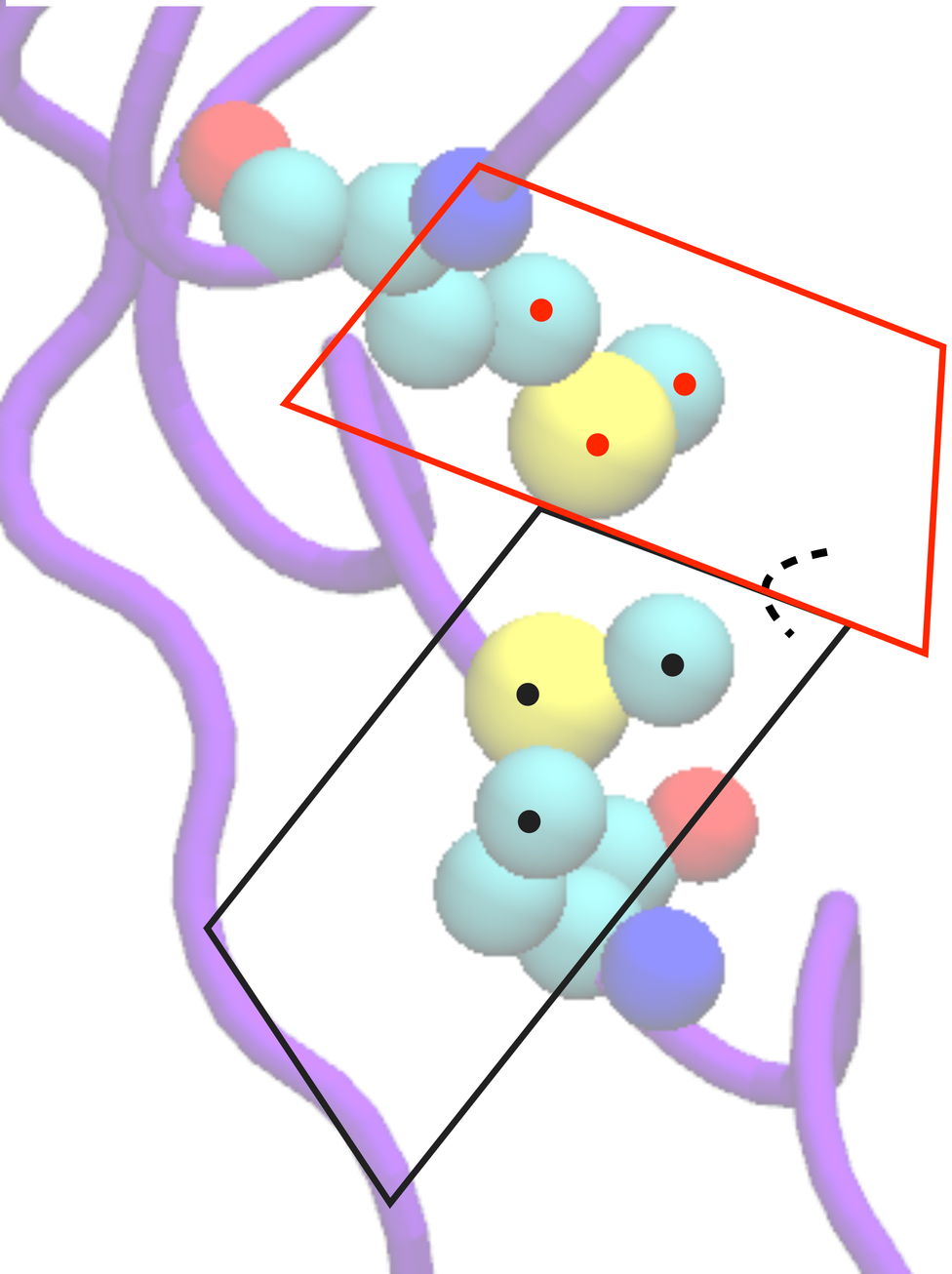
A21M Mutant



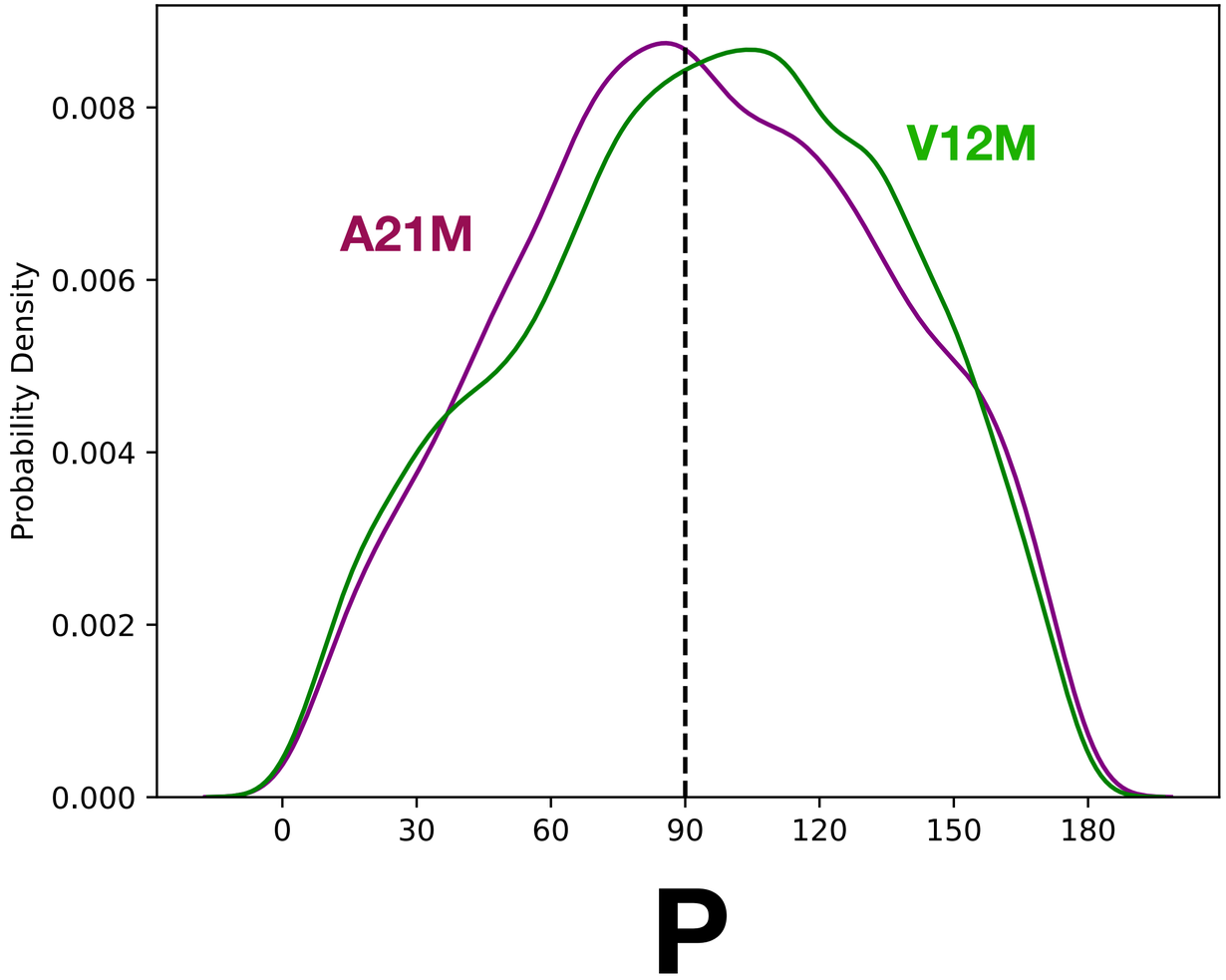



# Quantifying Methionine-methionine Interactions

# Identifying Met-Met interactions by geometry: P

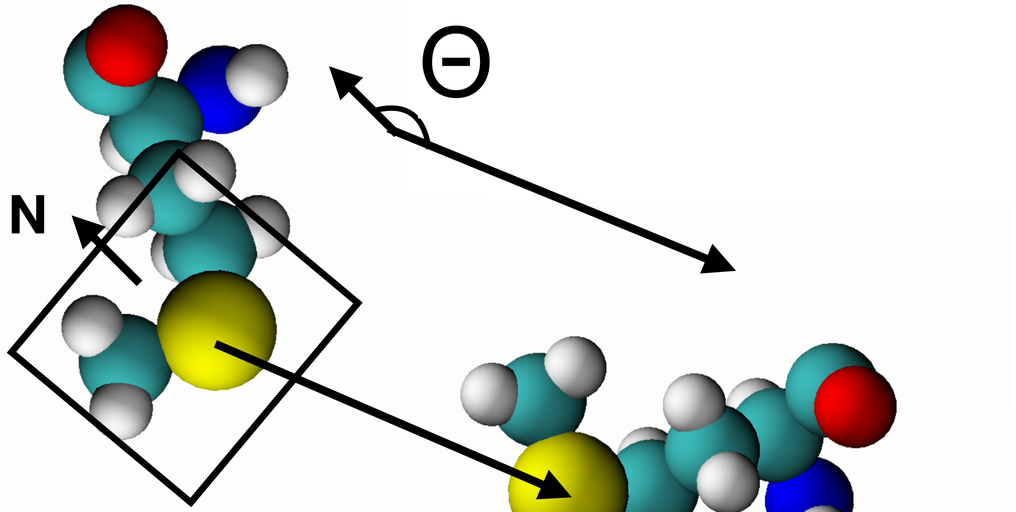


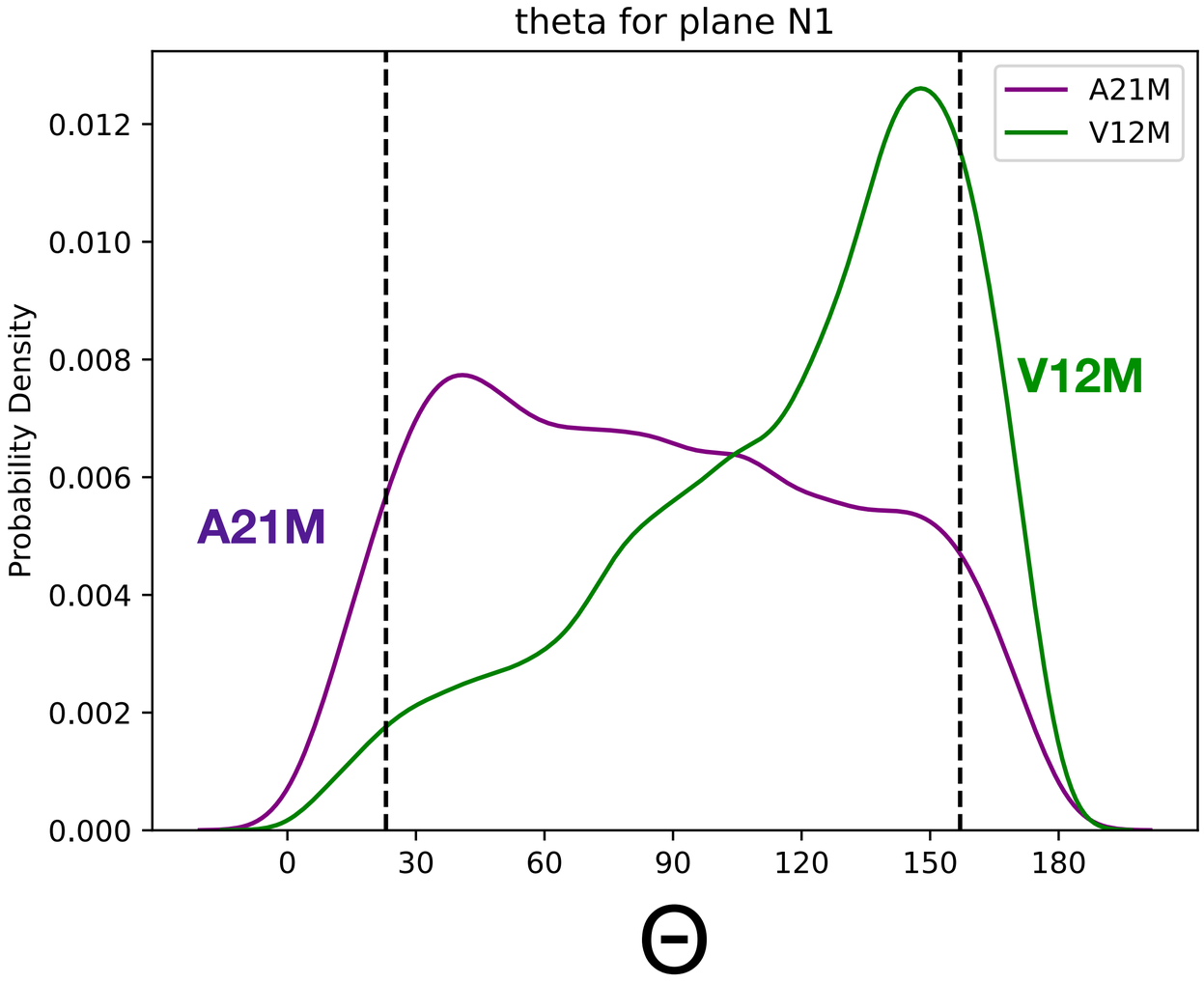
P




P

# Identifying Met-Met interactions by geometry: Θ



# Summary

- The addition of a second methionine increases contacts in Met-containing blobs in another IDP (Beta Amyloid)
- Geometric analysis of the methionine residues shows evidence of specific Met-Met interactions
- Results support a role for Met-Met interactions in IDPs

# Future Directions

- Polyalanine and polylysine chains with methionine
- REMD
- More intrinsically disordered proteins

# Acknowledgements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- Kaitlyn Bassi
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- Caliburn
- Busch Biomedical Society

# Questions?