

Structural Modeling of a Coding SNP in Subject Z

CBB 752 Final Project

May 18, 2017

Amino Acid Mutations

- Why Structural Modeling?
- SNPs might lead to changes in
 - Size
 - Charge
 - Hydrophobic effect
 - Potential energy

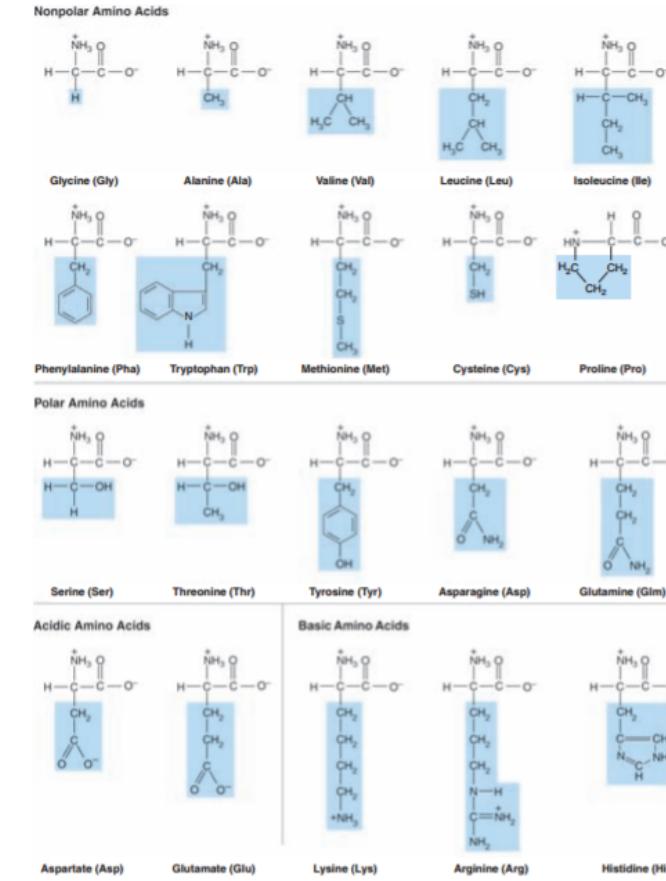
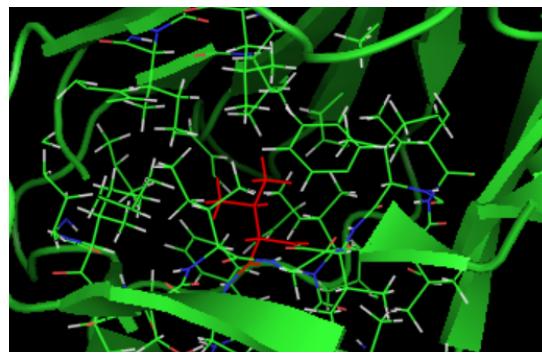


FIGURE 5.2

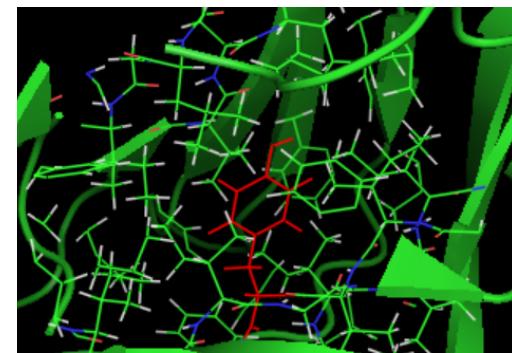
[Slide from Megan, Amber, and Krystle's presentation]

[McKee, T., & McKee, J. R. (2012). *Biochemistry: The molecular basis of life*. Oxford: Oxford University Press.]

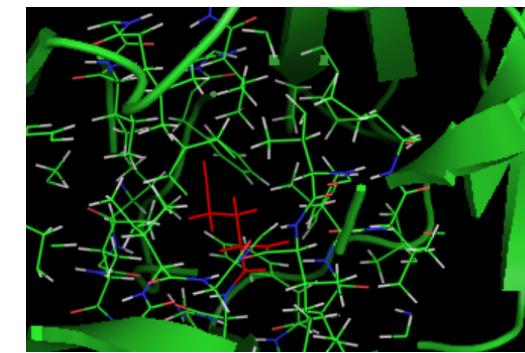
Favorable Mutations



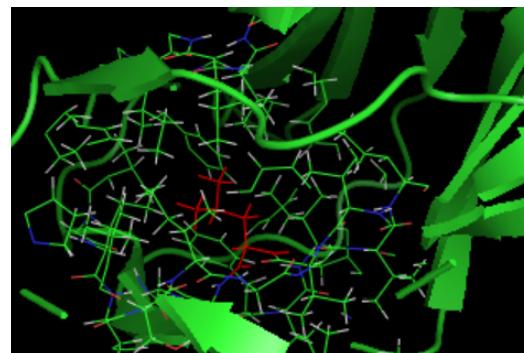
I35V
-2.775



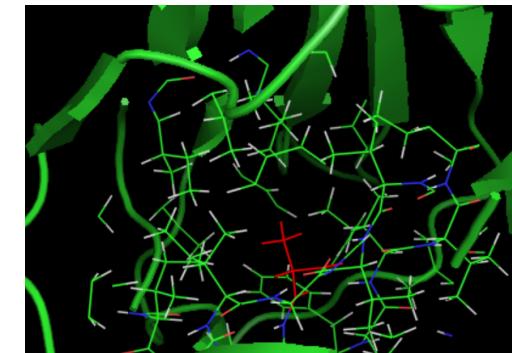
I35Y
-2.660



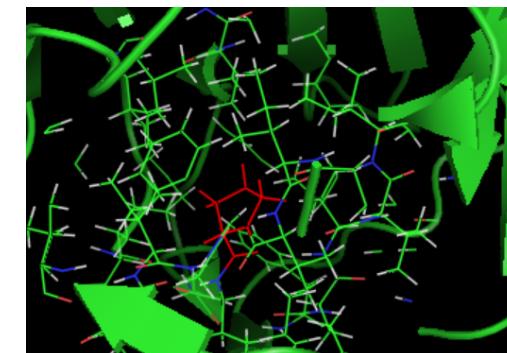
I35E
-2.652



I35L
-1.712



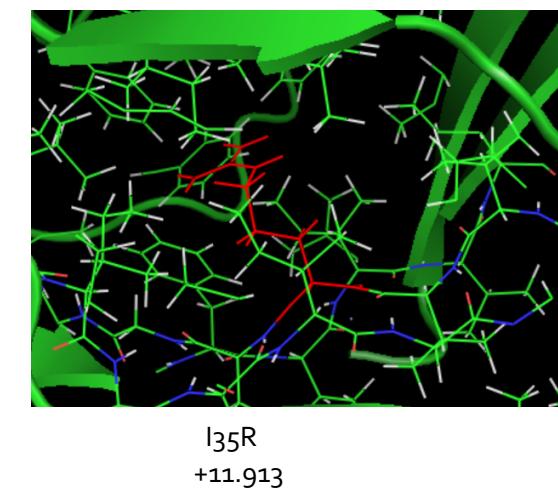
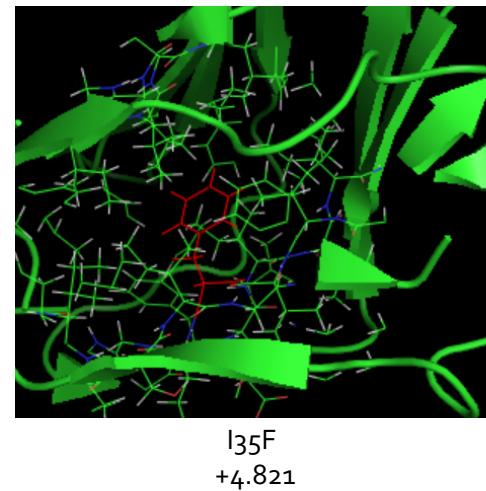
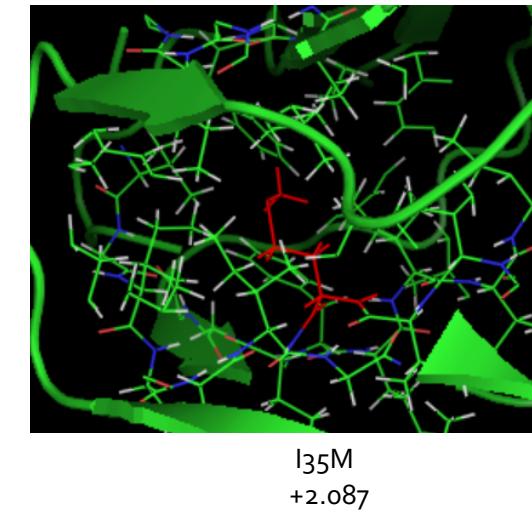
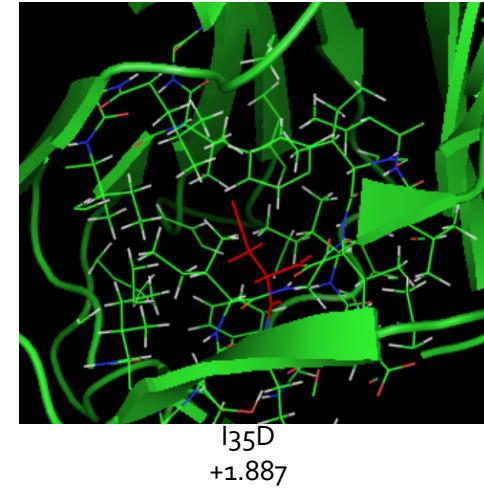
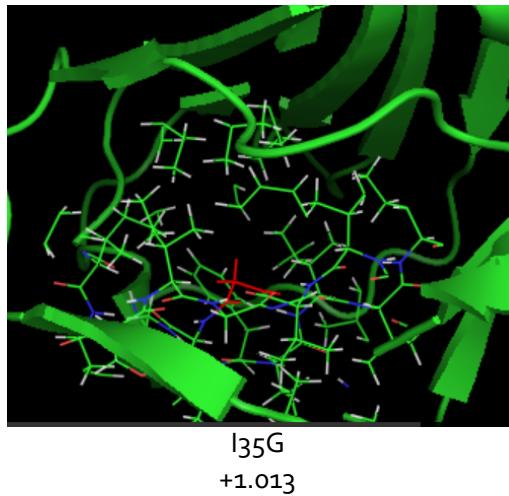
I35A
-1.097



I35P
-0.115

[Slide from Megan, Amber, and Krystle's presentation]

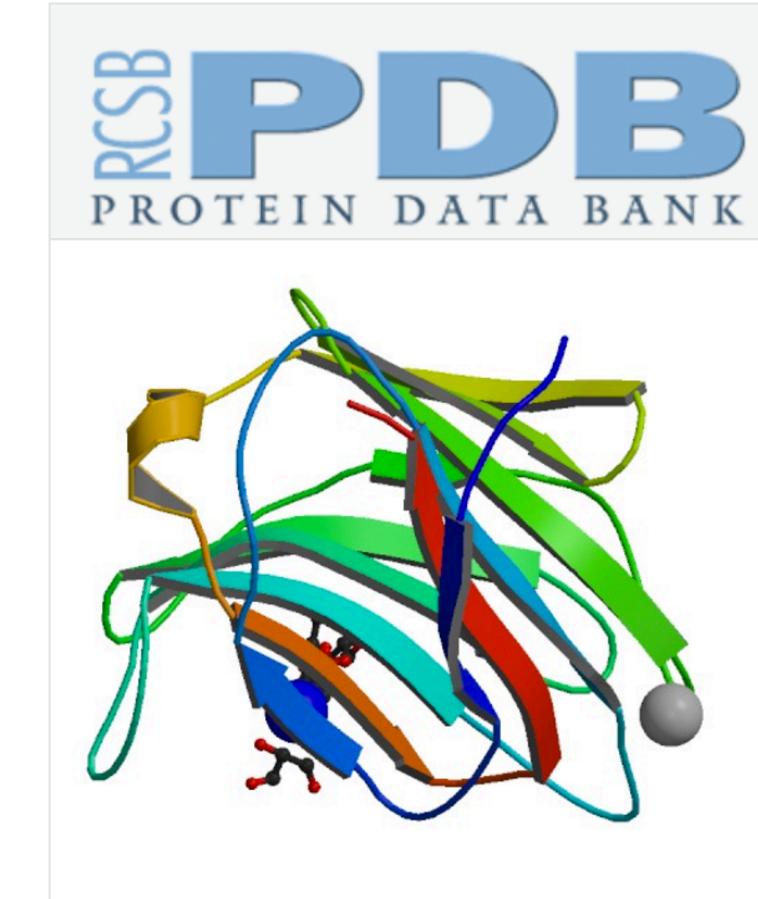
Unfavorable Mutations



[Slide from Megan, Amber, and Krystle's presentation]

Introduction

- The gene 3VKO codes for the Galectin-8 protein
- During infections, Galectin-8 is thought to restrict the proliferation of pathogens by targeting them for autophagy
- We Analyze it in Carl's genome for 4BMB (galectin-8)



F19 Mutation

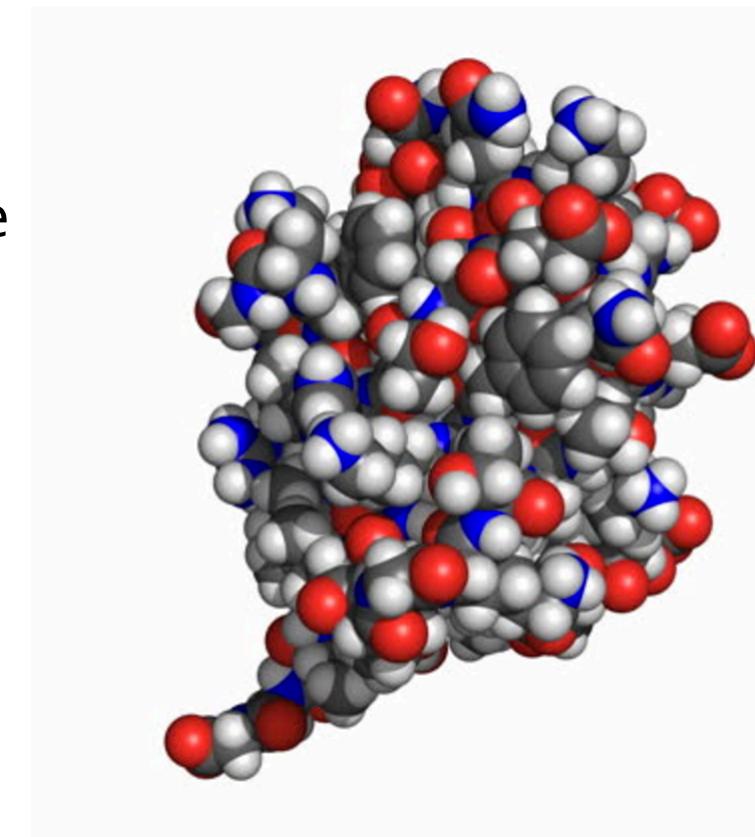
- From an initial side-chain chemistry standpoint, this mutation should be relatively minor, as it occurs away from the binding pocket
- The residue does not appear to play a major role in the interaction of the two domains of the protein



[http://images.medicaldaily.com/sites/medicaldaily.com/files/styles/teaserheadline/public/2016/02/04/genetic-mutation.jpg]

F19Y

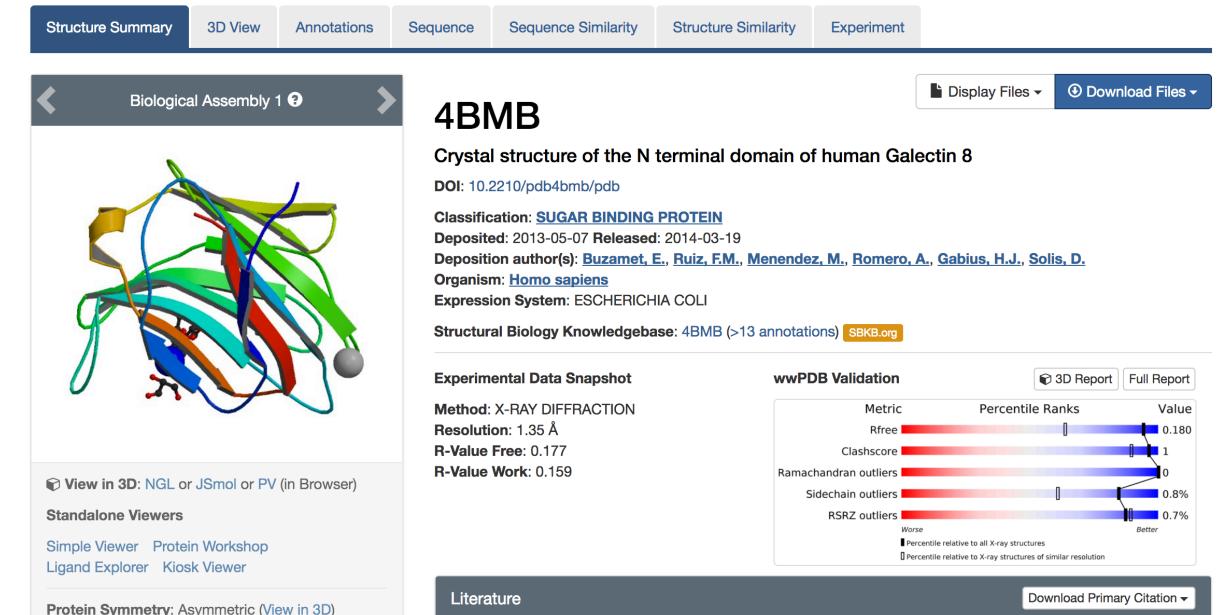
- From a space-filling perspective, the tyrosine mutation is about as large as phenylalanine
- May disrupt the structural stability of the protein, but not majorly



<https://www.shutterstock.com/video/clip-752206-stock-footage-insulin-molecule-rotating-space-filling-model-seamless-loop-insulin-is-a-pancreatic-hormone.html>

Pipeline

- 4BMB PDB file
- Six steps
 - Relaxing the protein PDB file
 - Repacking the structure
 - Calculating Delta G of the wild type protein
 - Repacking the structure with a point mutation at position 19
 - Calculating Delta G' of the mutated protein
 - Calculating the change in binding energy.



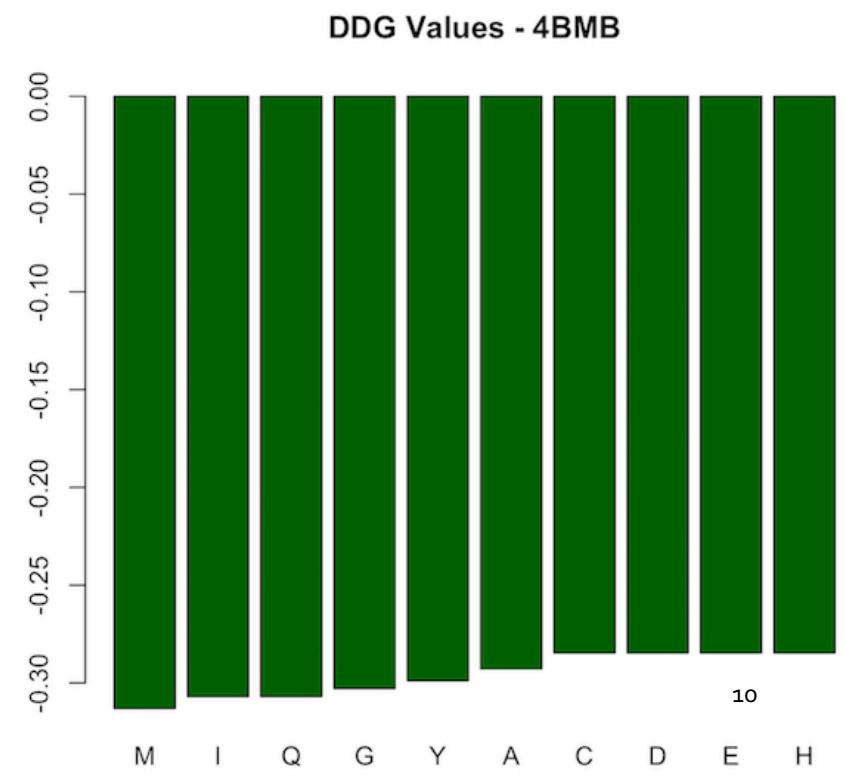
Pipeline

- Rosetta 2017.08
- Suite of algorithms for computational modeling and analysis of protein structures
- Introducing mutations

```
NATAA
EX 1 EX 2
USE_INPUT_SC
start
#Pick M mutation at residue 19 (on peptide A)
19 A PIKAA M
```

Pipeline

- 10 AA point mutations at position 19 of 4BMB
- All stabilizing ddG < 0
- Most stabilizing: M
- Least stabilizing: C, D, E, and H



Pipeline

- Why M?
- M & T are “very hydrophobic”
- Other AAs among chosen 10 are either hydrophilic or “hydrophobic”

inside **H** (hydrophobic)

outside **P** (polar)

	At pH 2 ^a	At pH 7 ^b	
Very Hydrophobic			
Leu	100	Phe	100
Ile	100	Ile	99
Phe	92	Trp	97
Trp	84	Leu	97
Val	79	Val	76
Met	74	Met	74
Hydrophobic			
Cys	52	Tyr	63
Tyr	49	Cys	49
Ala	47	Ala	41
Neutral			
Thr	13	Thr	13
Glu	8	His	8
Gly	0	Gly	0
Ser	-7	Ser	-5
Gln	-18	Gln	-10
Asp	-18		
Hydrophilic			
Arg	-26	Arg	-14
Lys	-37	Lys	-23
Asn	-41	Asn	-28
His	-42	Glu	-31
Pro	-46	Pro	-46 (used pH 2)
		Asp	-55

^apH 2 values: Normalized from Seenda et al., J. Chrom. 676: 139-153 (1994).

^bpH 7 values: Monera et al., J. Pept. Sci. 1: 319-329 (1995).

Pipeline

- Changes in stability might lead to changes in protein function

BMC Bioinformatics



Research

Open Access

Correlating protein function and stability through the analysis of single amino acid substitutions

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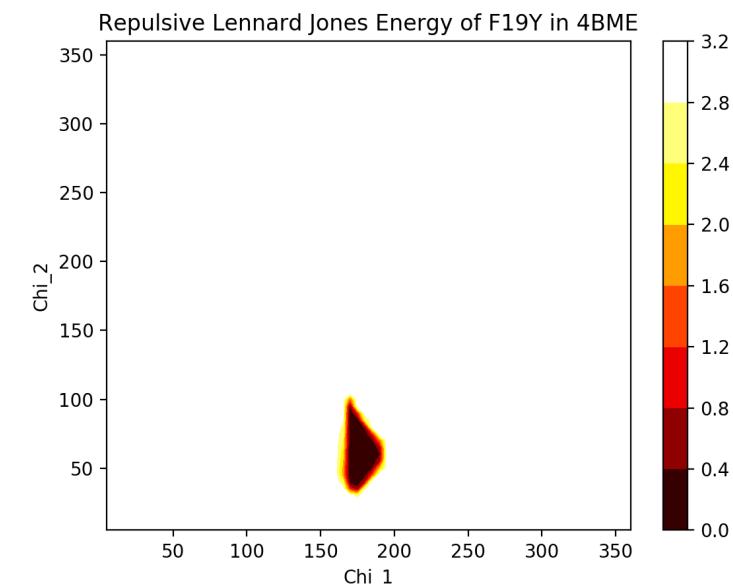
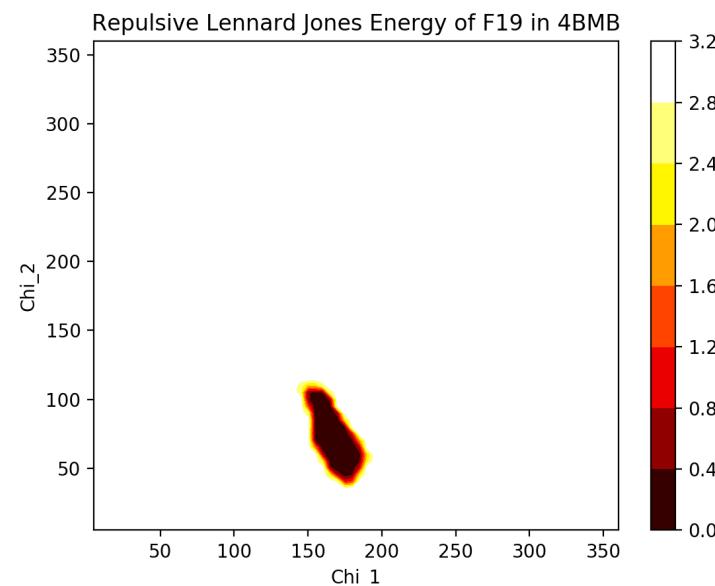
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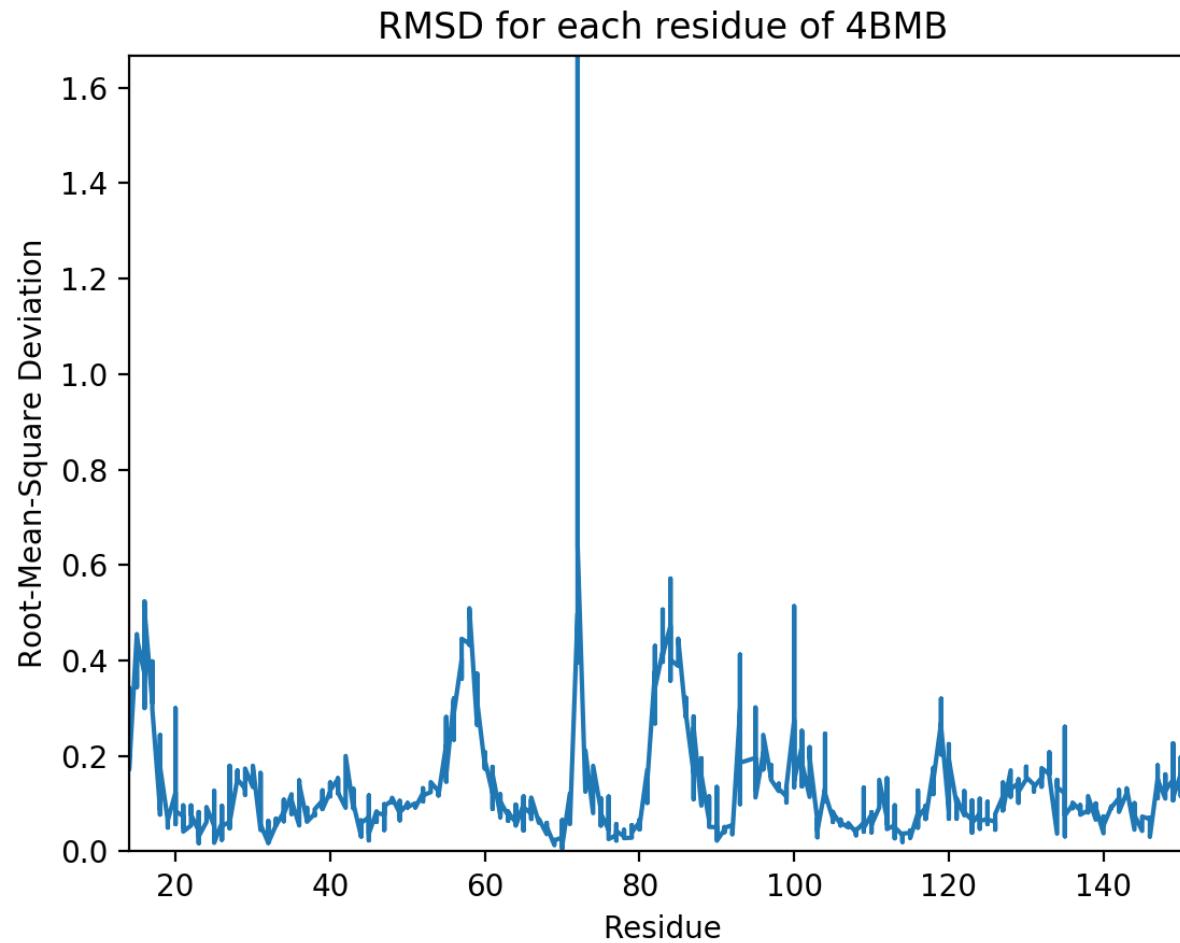
* Corresponding author

WT vs. Mutant: Repulsive Energy

- Very similar energy dips
- Dihedral angles of Y should roughly match those of F
- -OH of Y probably decreases allowable conformations



WT vs. Mutant: RMSD



- Take backbone heavy atoms C, N, O, Ca
- Mean distance between atoms in WT vs Mutant

END | Thank You