

# Good Fences Make Distant Neighbors: Determining the Effect of Local Sequence Context on Met-Met interactions.



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## Abstract

Residue-residue interactions extend beyond just oppositely charged residues; some hydrophobic residues can also undergo favorable interactions. One example of this kind of interaction occurs between two methionine residues. Recently, a study on the BDNF prodomain identified that the disease-causing effects of the Val66Met mutation stems from Met-Met interactions increasing the probability of contact between contiguously hydrophobic regions (termed “blobs”) not previously in contact [1]. However, there is a lack of knowledge about how widespread Met-Met interactions are in proteins, or how different local sequence contexts influence the rate of these Met-Met interactions. In this poster, we measure the probability of contact between two methionine residues in three blob types: hydrophobic, polar, and charged. To do this, we analyze molecular dynamics simulations and detect contacts by testing for established geometric configurations. We find that blob type influences the contact probability between methionine residues in both our Beta Amyloid and our short peptide simulations and ultimately demonstrate that it is your neighbors that can make (or break) whom you come into contact with.

## Background and Approach

- Intrinsic disorder is found in approximately 30% of all proteins in the eukaryotic proteome [2]
- A previous study done by our lab on the Val66Met mutation to the BDNF pro domain used our blobulation algorithm to group residues to quantify tertiary (“blob”) contacts [1].
- This study found that Met-Met interactions in the mutant changed the frequency of contacts between methionine-containing blobs.
- Methionine-methionine (Met-Met) interactions are enriched in the structures of folded proteins [3] and can be defined geometrically [4]
- The effect of local sequence context on Met-Met interactions is unknown.

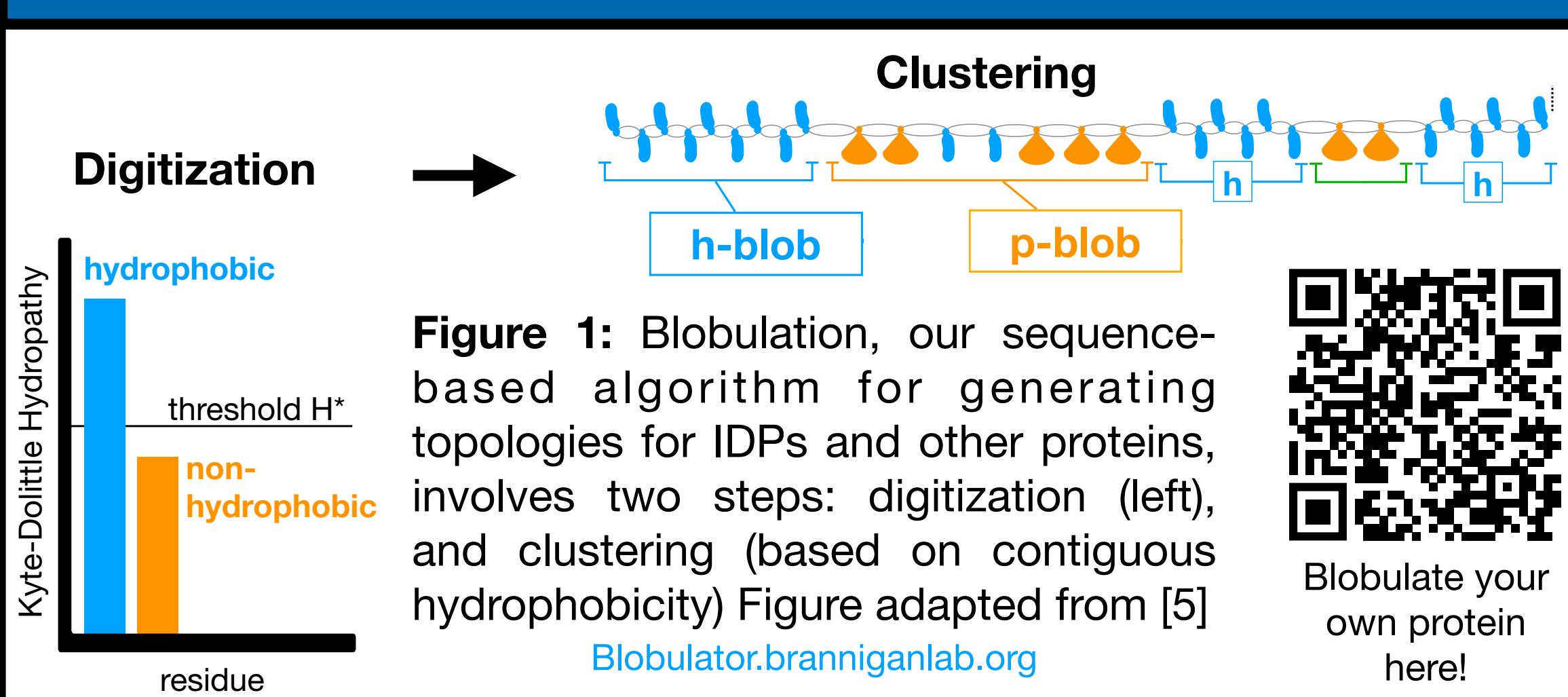
### Research Questions:

- Do Met-Met interactions change the blob-contact rates in other proteins besides the BDNF prodomain?
- Are Met-Met interactions context-dependent?

### Approach: Atomistic simulations on...

- A second IDP - Beta Amyloid (1-42) wild type and mutants to see if Met-Met interactions are generalizable to other IDPs
- Short peptides containing two methionines to investigate the effect of local sequence context, varying:
  - Spacing between methionine residues
  - Peptide composition (hydrophobic, polar, charged)

## Blobulation

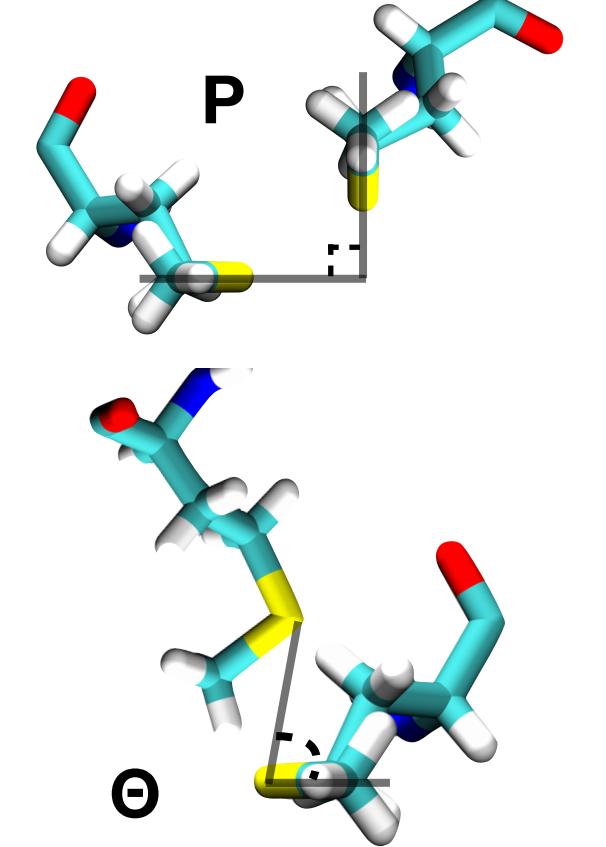


**Figure 1:** Blobulation, our sequence-based algorithm for generating topologies for IDPs and other proteins, involves two steps: digitization (left), and clustering (based on contiguous hydrophobicity) Figure adapted from [5]

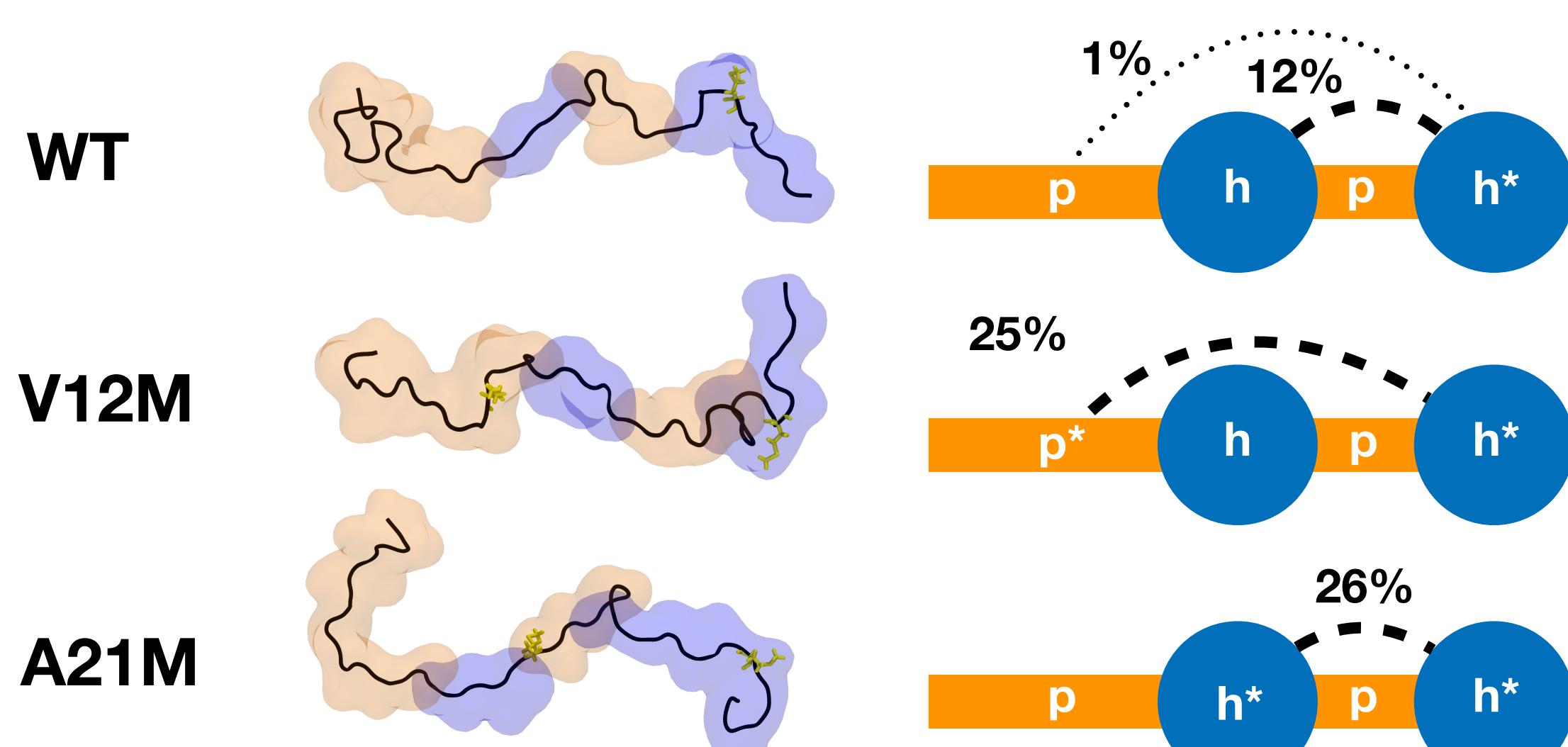
[Blobulator.branniganlab.org](http://Blobulator.branniganlab.org)

## Detecting Met-Met Interactions

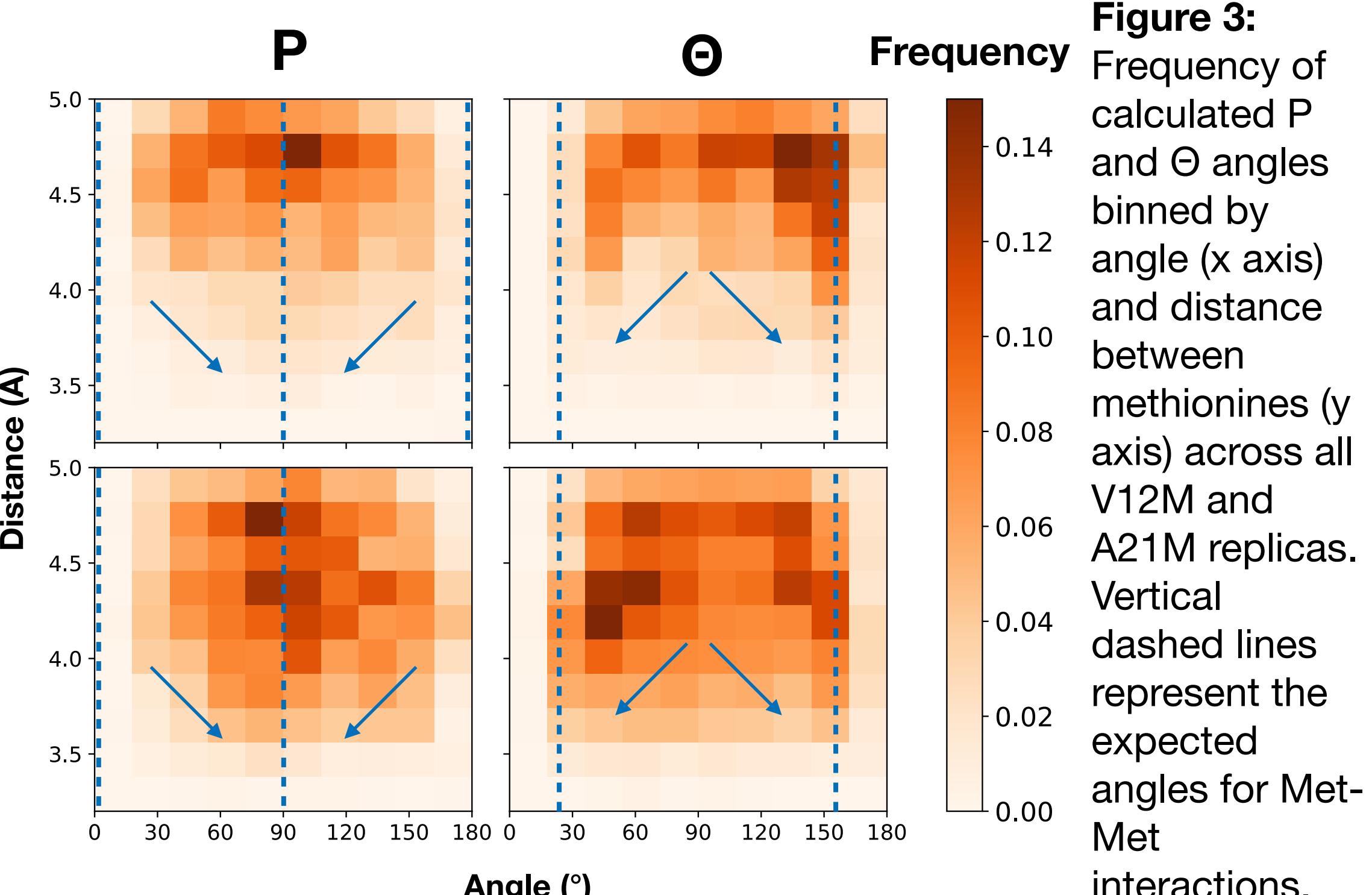
- Geometric definitions for detecting specific Met-Met interactions have been defined by Gomez-Tamayo et al. [3]
- For each methionine residue, the sulfur and the two adjacent carbons are treated as points, which form a plane.
- P angle: Angle between two planes. **Expected: 0°, 90°**
- Θ angle: Angle between vector created by two sulfurs and each plane. **Expected: 23°, 157°**



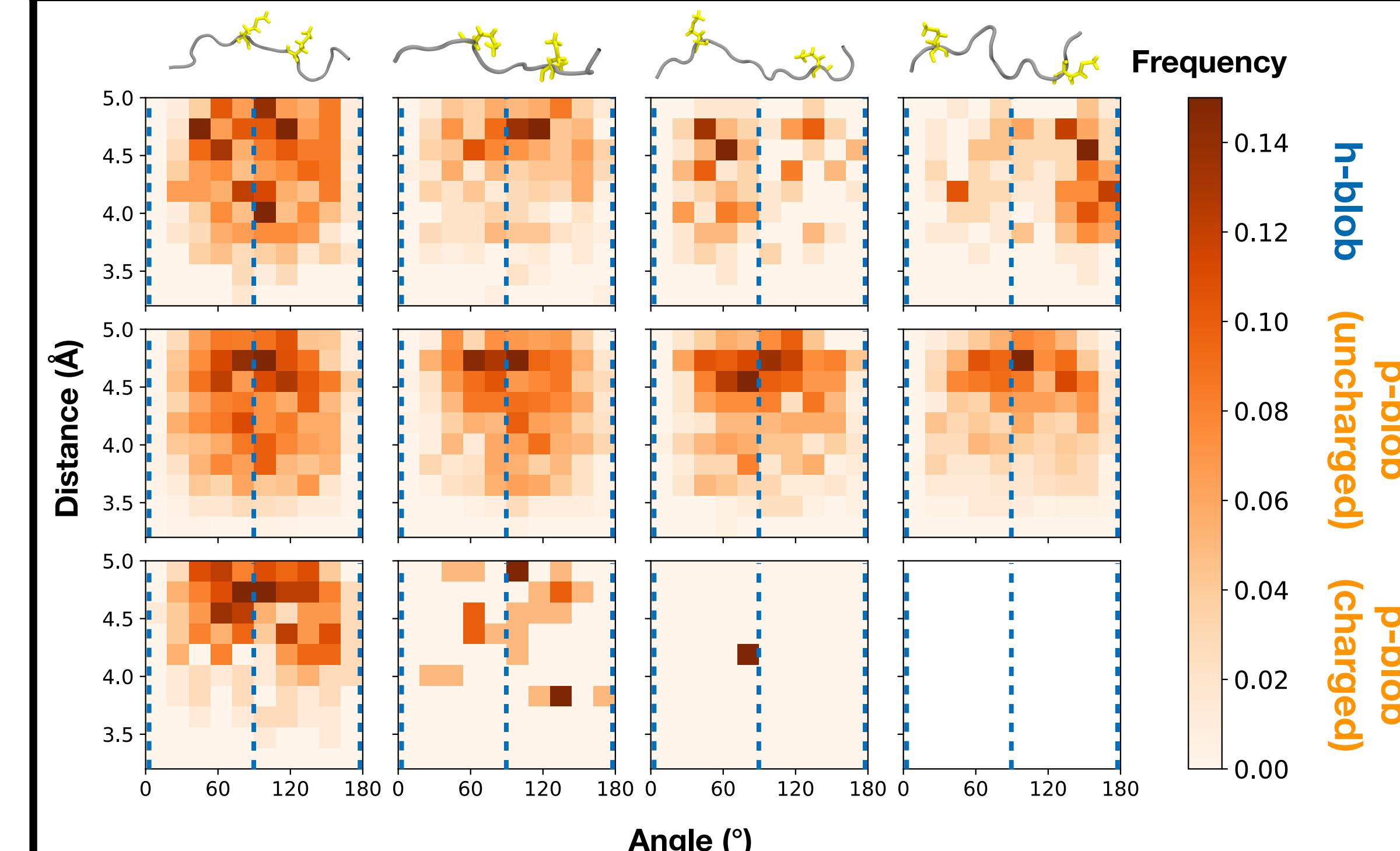
## Tertiary Contact Shifts



**Figure 2:** Contacts between blobs. Dashed lines represent the percentage of frames where blobs are in contact. An asterisk (\*) indicates that there is a methionine in the blob



## Local Sequence Context Effects



**Figure 4:** Frequency of calculated P angles binned by angle (x axis) and distance between methionines (y axis) for met-poly-X simulations. Vertical dashed lines represent the expected angles for Met-Met interactions.

## Summary

- Met-Met interactions change the blob contact frequencies in Beta Amyloid mutants, which provides further evidence that Met-Met interactions in IDPs can cause tertiary-level changes
- Met-Met interactions are context dependent. They occur at different frequencies if surrounded by hydrophobic, polar, and charged residues.

## References

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## MD Simulations

- Software: GROMACS 5.1.2 [3], Force Field: Amber99sb-ildn-q [6]
- Temperature: 300K
- AB simulations: Wildtype (3 replicas), V12M (5 replicas) and A21M (5 replicas) mutants. 5μs.
- Met-poly-X simulations: 3μs, 1 replica each. Methionines 2, 4, 6, and 8 residues apart

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