



Knots on the Brain: Finding Knots in Proteins

Elizabeth Whalen

Advisor: Dr. Eric Rawdon

University of St. Thomas – St. Paul, Minnesota

What is a mathematical knot?

- A **mathematical knot** is a closed curve in 3-dimensional space, which can be visualized in 2D with a knot diagram
- Open vs closed knots
- Knots can be categorized by invariants like **crossing number**, or the smallest number of crossings in any diagram of the knot

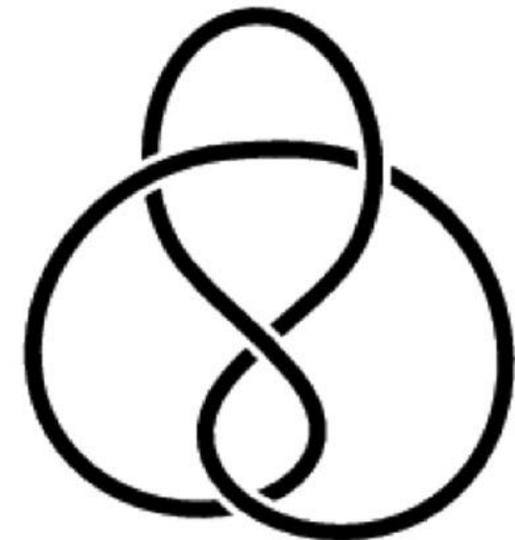
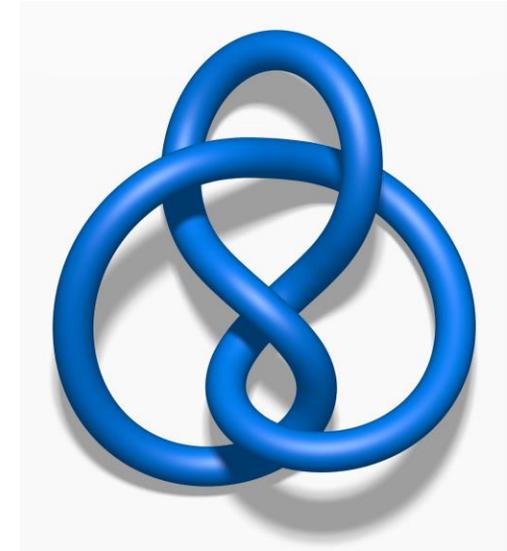


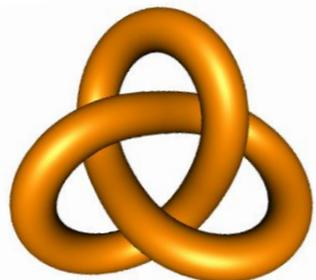
Figure eight (4_1) Knot

A larger crossing number generally means a more complicated knot:

The 0_1 "unknot"



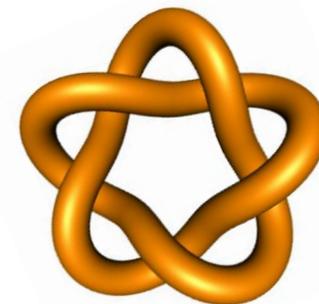
The 3_1 "trefoil knot"



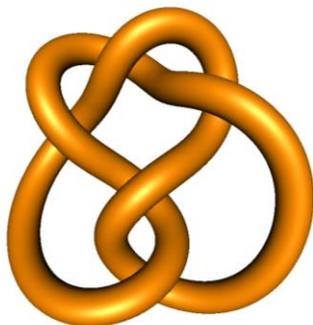
4_1



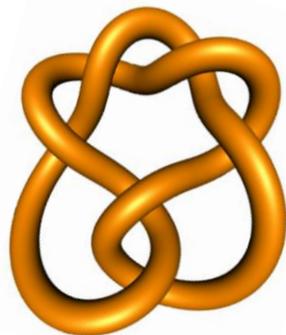
5_1



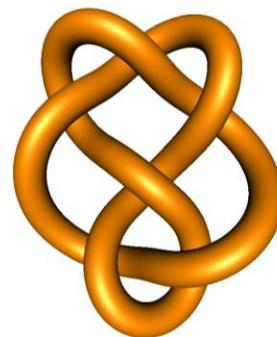
5_2



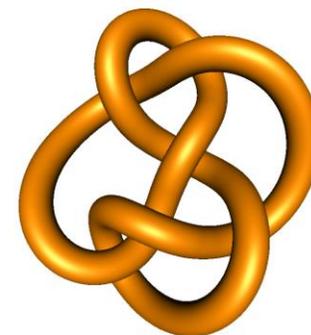
6_1



6_2

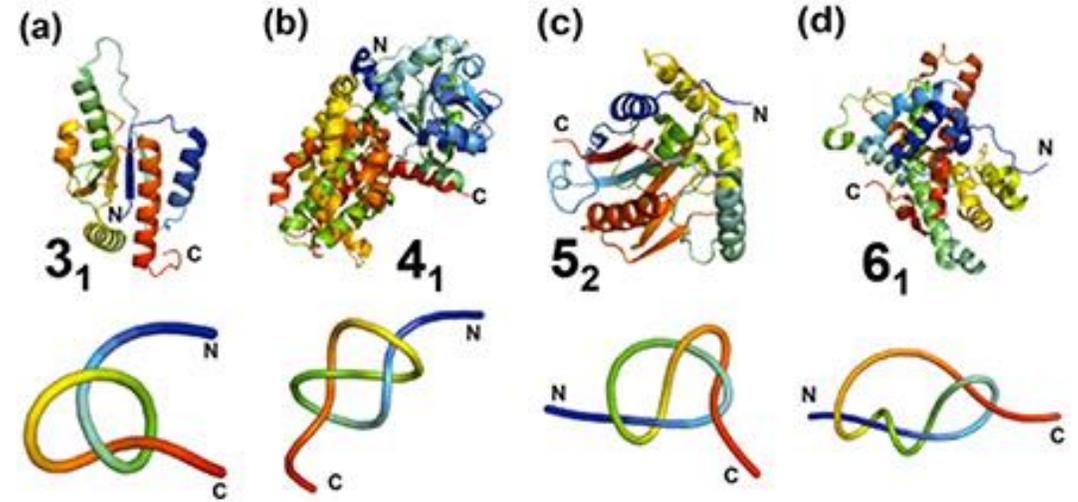


6_3



Knotted Proteins

- Knots have been found in the backbones of some protein chains
- For example, Ubiquitin C-terminal hydrolase L1 (UCH-L1):
 - Makes up 1-5% of total neuronal protein
 - UCH-L1 dysfunction is linked to Alzheimer's Disease
 - One of the most complicated knotting structures found so far in proteins



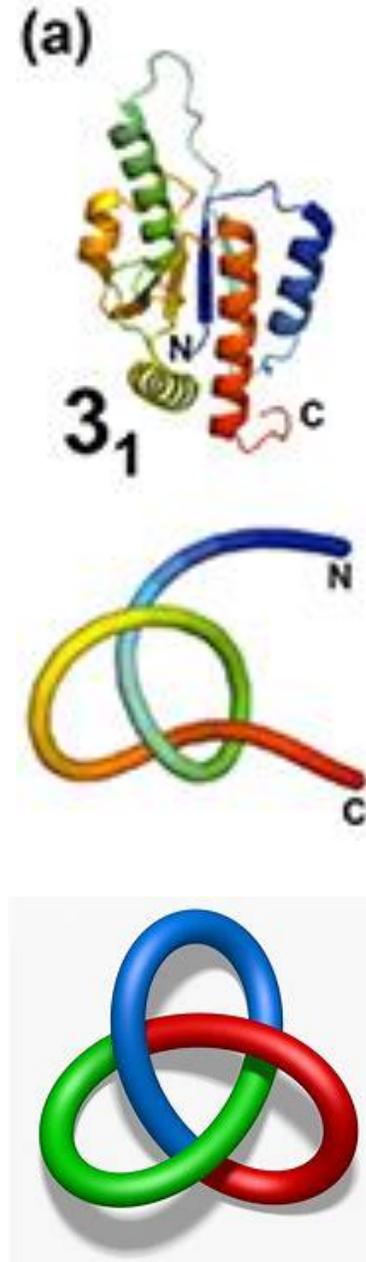
UCH-L1 knotted protein



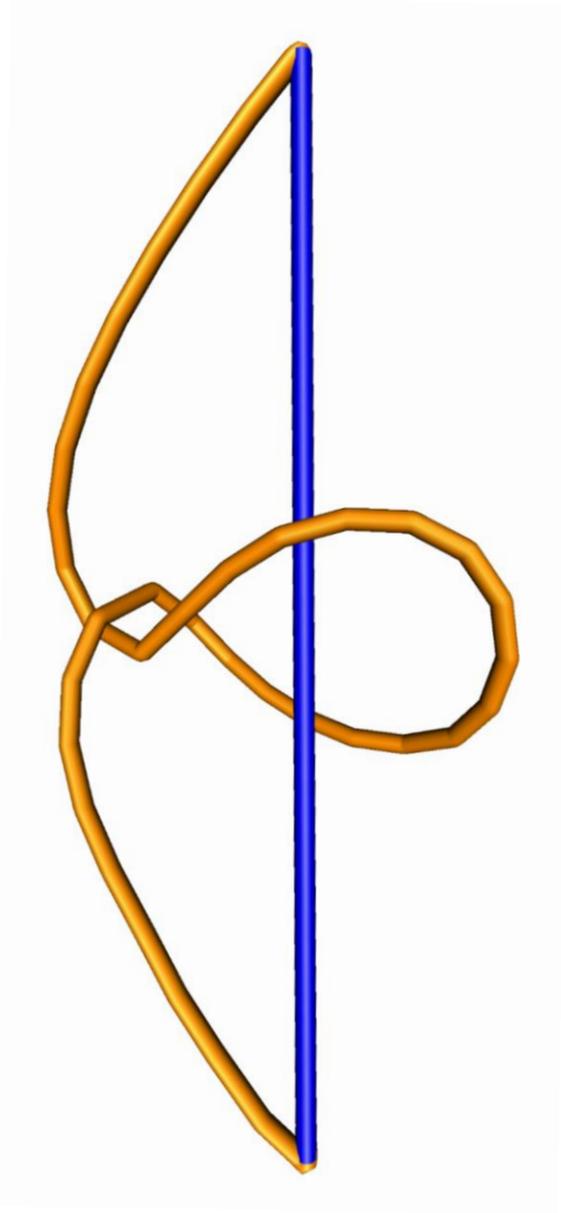
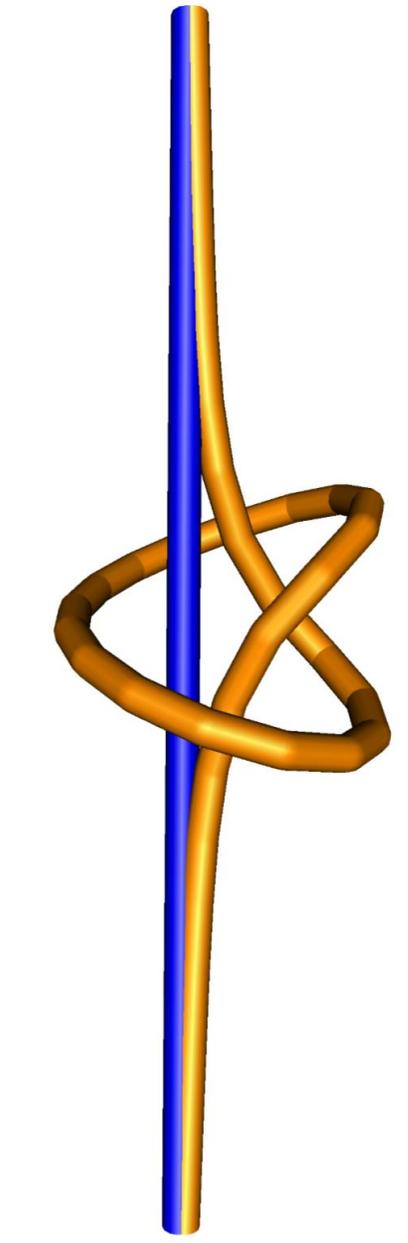
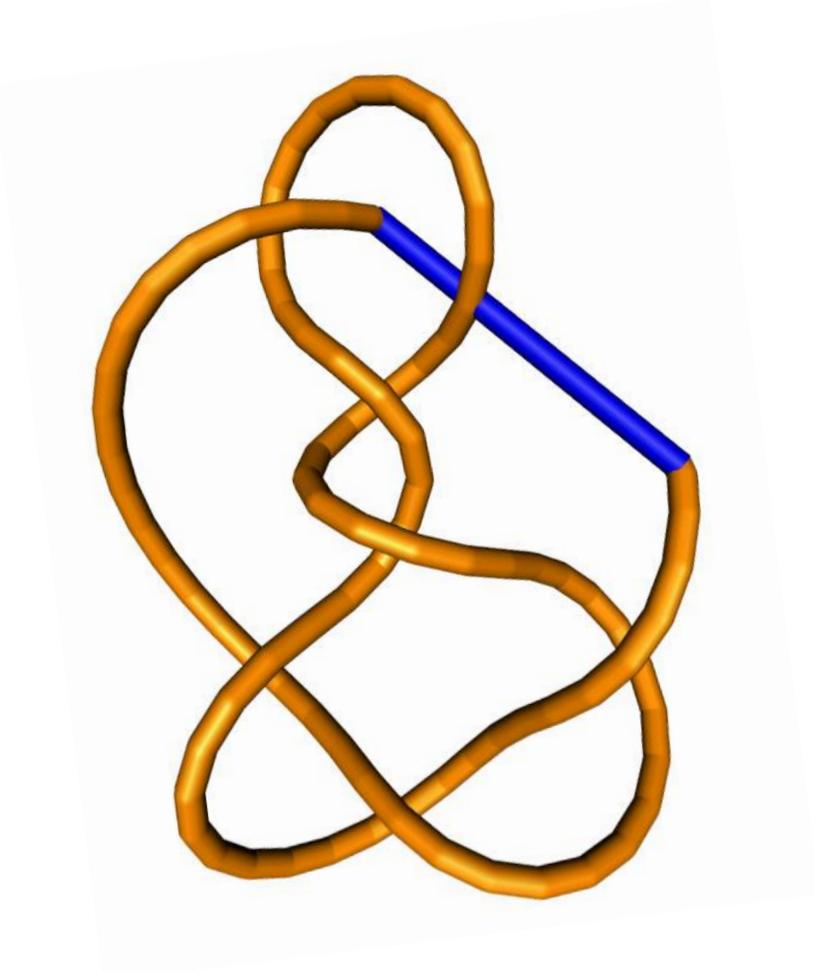
- Researchers believe that the location of the knots could provide critical information to understand this relationship

However...

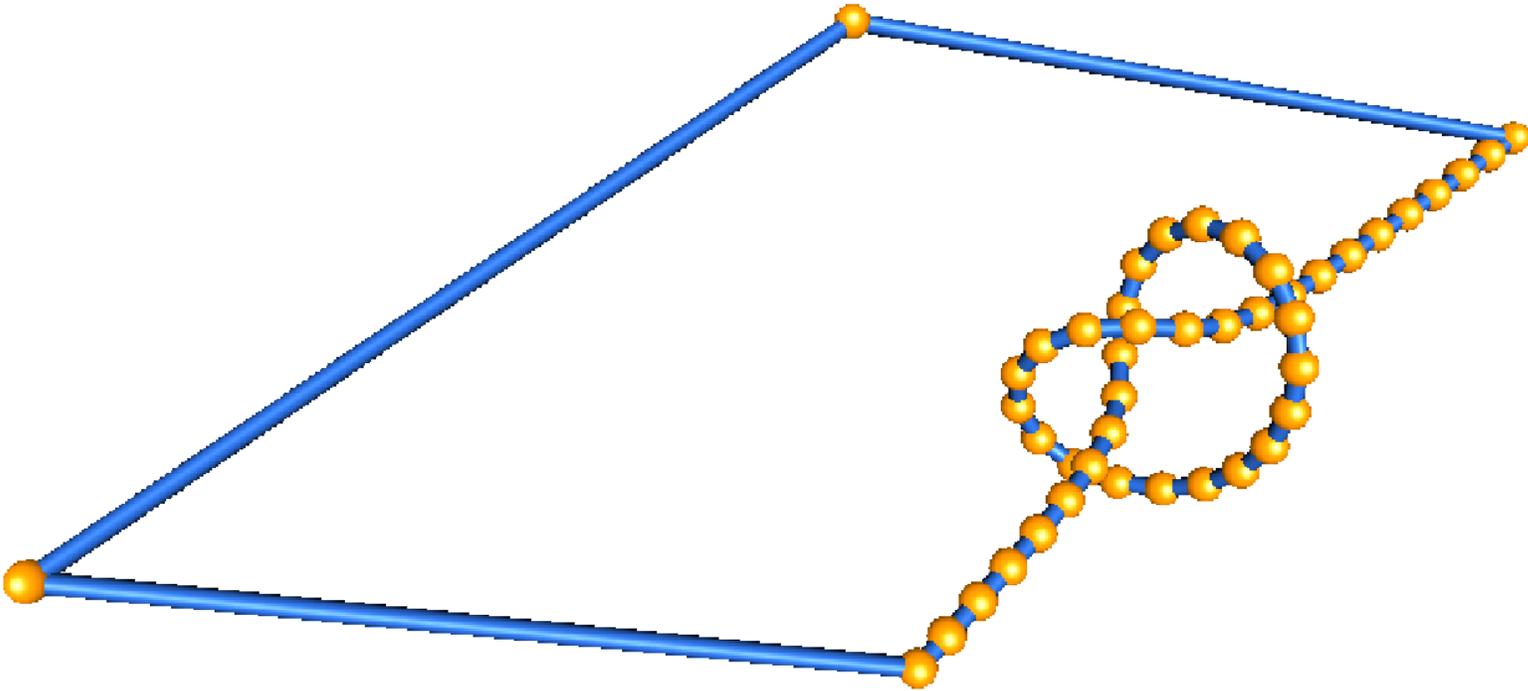
- The knots found in proteins are open knots
- Traditional knot theory deals with closed knots
- Next, characterize entanglement in open chains



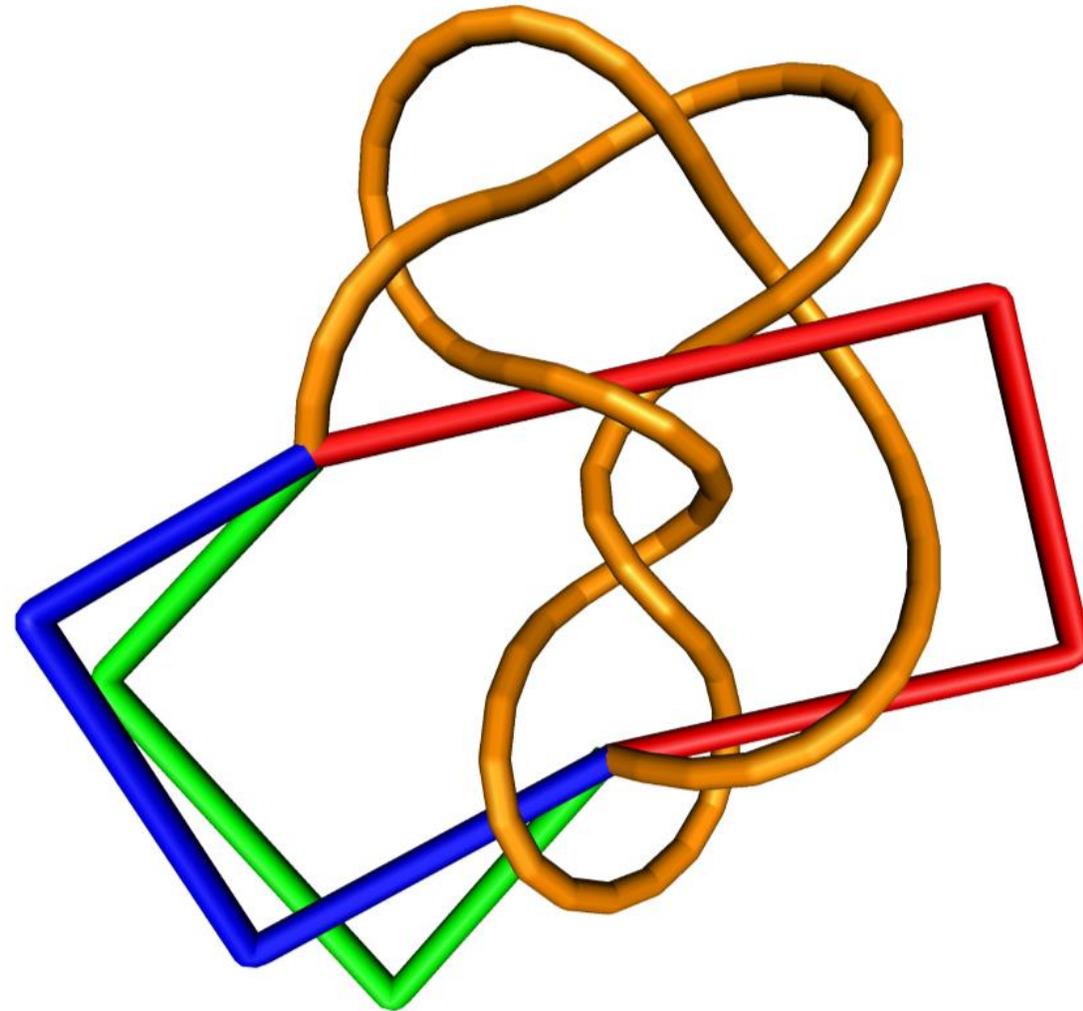
Direct connection (easy but bad)



What if we shoot the endpoints out to infinity before connecting them?

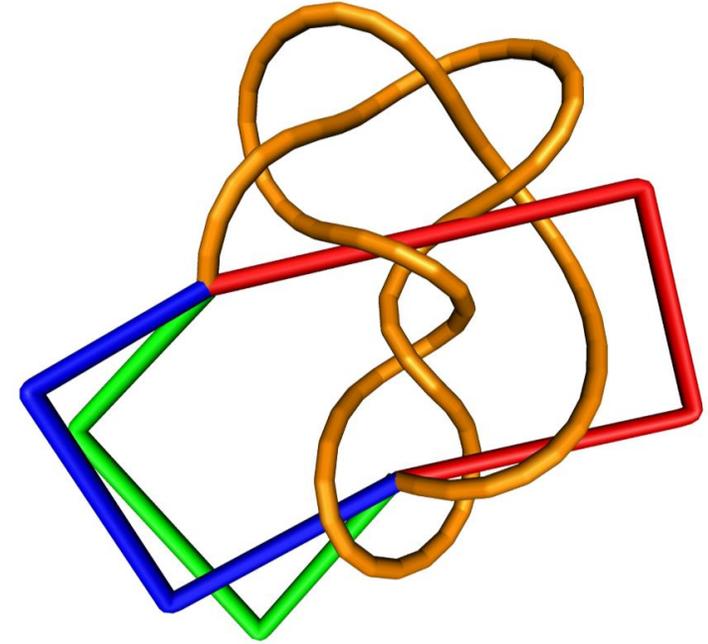


Multiple directions



For any open chain:

1. Do this process in 100 different directions
2. Identify knot type for each direction
3. You get a distribution of knot types for the open chain
4. Highest proportion \longrightarrow knot type



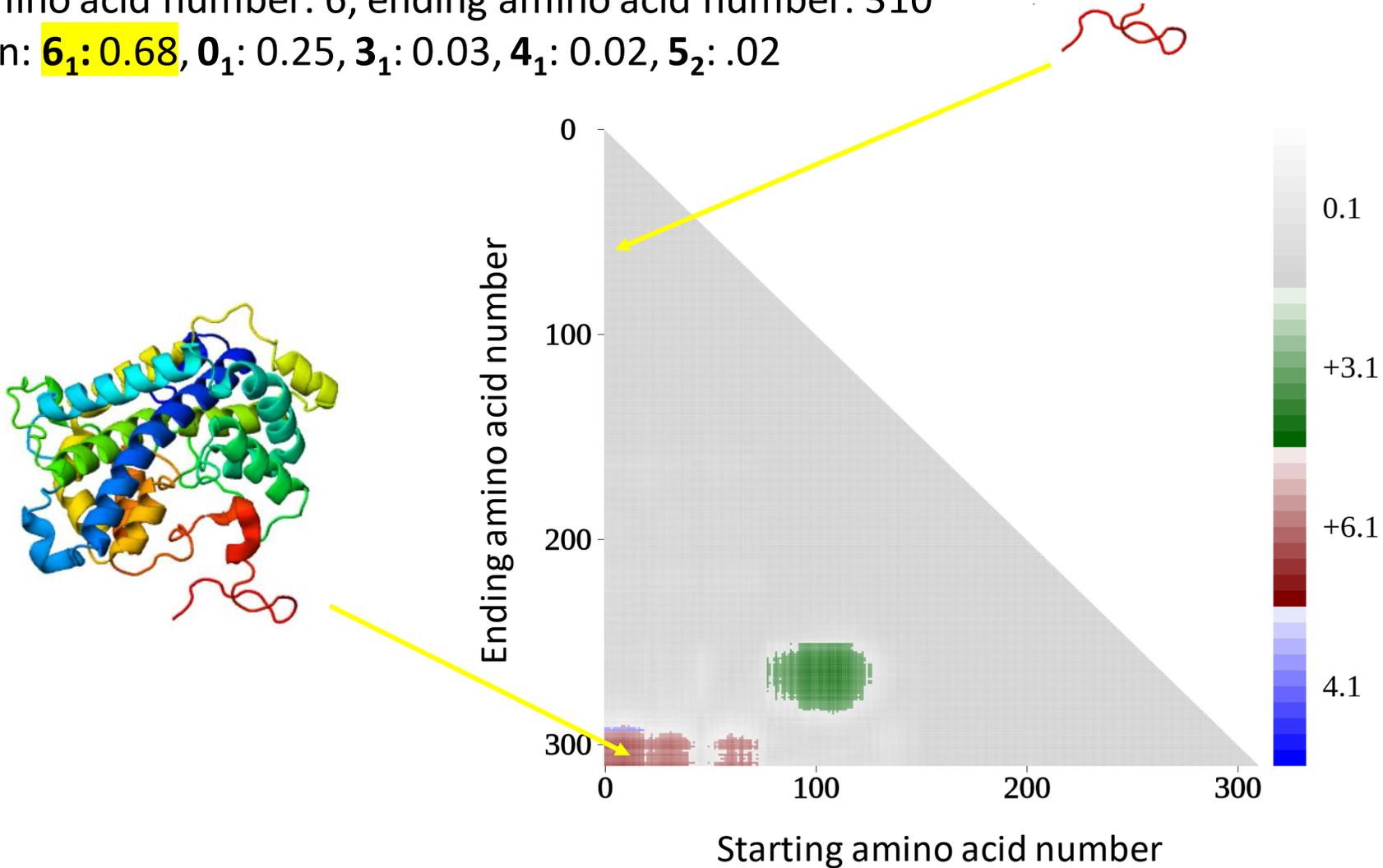
Location

- The resulting knot type also varies depending on where on the protein you are doing this process
- For each starting and ending amino acid number, there is an open knotted subchain
- Trying to find connections between location and knotting

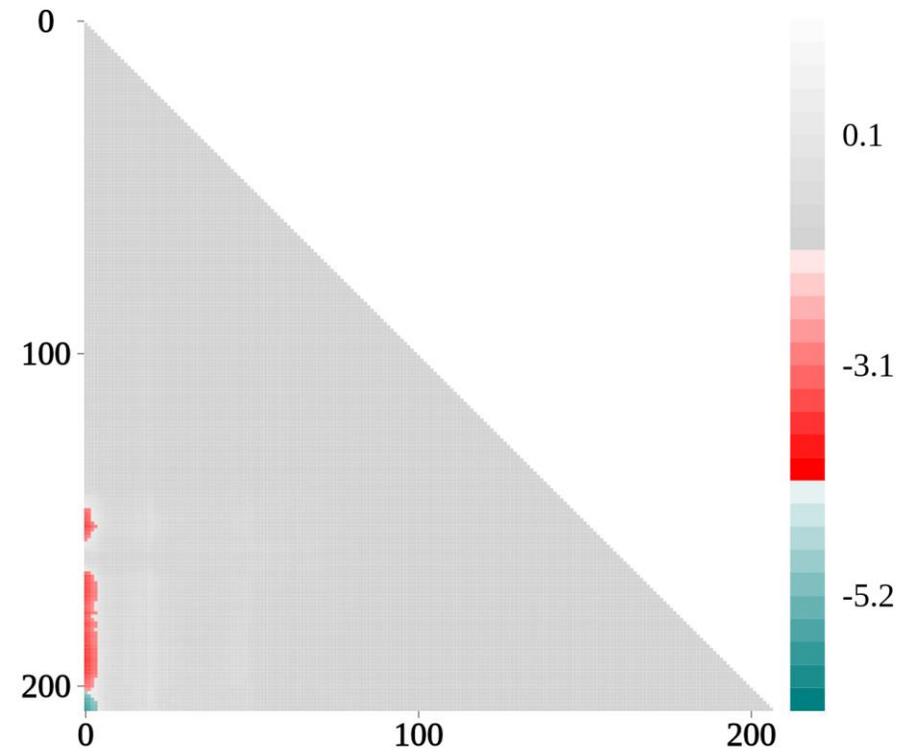
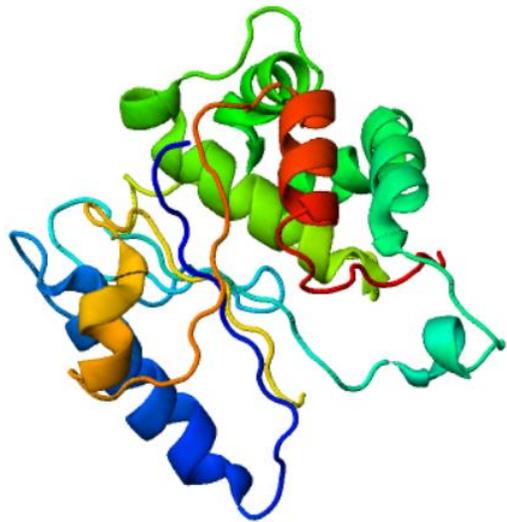
Example: protein 3BJX-A

Starting amino acid number: 6, ending amino acid number: 310

Distribution: **6₁: 0.68**, 0₁: 0.25, 3₁: 0.03, 4₁: 0.02, 5₂: .02



Protein UCH-L1 (2WE6-A)



An alternative way to classify

- Frequently, the greatest proportion that resulted was the unknot, but this proportion was < 0.5
 - Ex: 1 202 of UCH-L1: 0.1: 0.33, 3.1: 0.32, 5.2: 0.32, 5.1: 0.02, 7.3: 0.01
- Should we really be classifying these knots as unknots despite there being more "knotting" than "unknotting" going on?

Accumulation method example

Protein 3BJX-A: Location: 1 290

•Original/proportional distribution:

•**0₁: 0.44**

•**4₁: 0.3**

•**6₁: 0.21**

•**3₁: 0.05**

•Accumulation method:

•**3₁: 0.56 = 0.3 + 0.21 + 0.05**

•**4₁: 0.51 = 0.3 + 0.21**

•**6₁: 0.21**

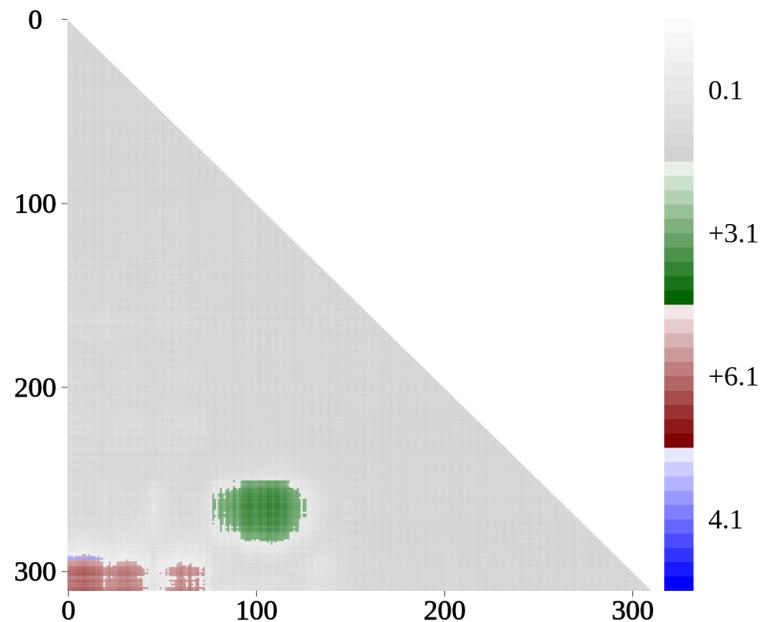
Protein 3BJX-A

Location: 1 290

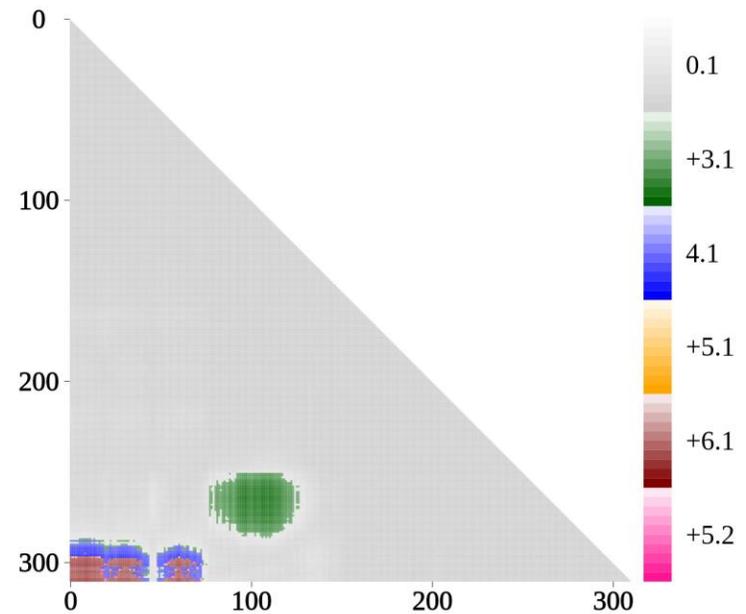
Original/proportional distribution: $0_1: 0.44$, $4_1: 0.3$, $6_1: 0.21$, $3_1: 0.05$

Accumulation method: $3_1: 0.56 = 0.3 + 0.21 + 0.05$, $4_1: 0.51 = 0.3 + 0.21$, $6_1: 0.21$

Proportion method

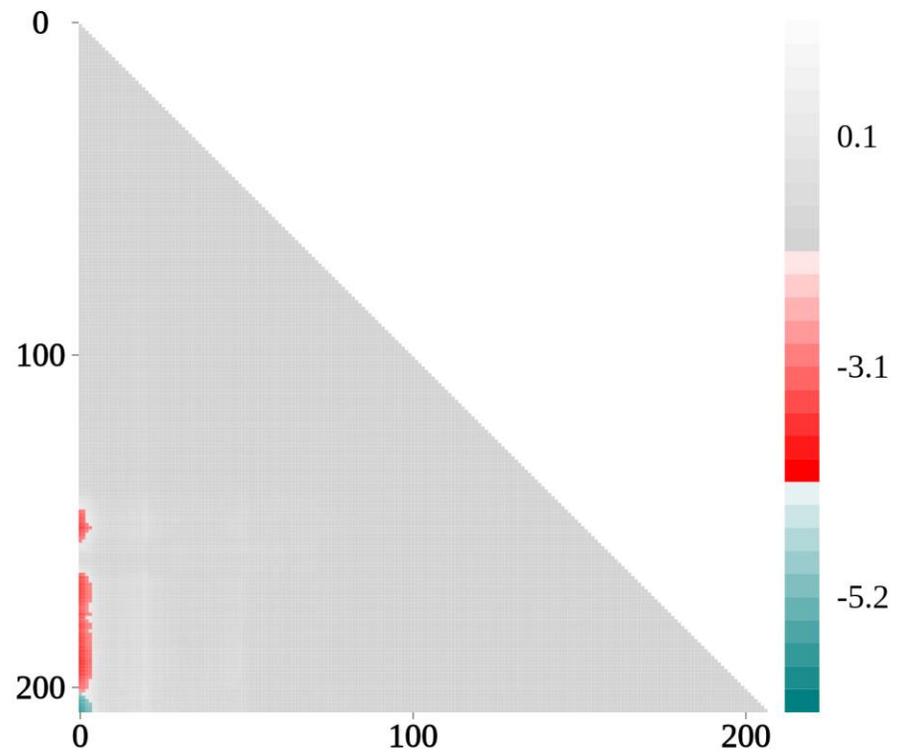


Accumulation method

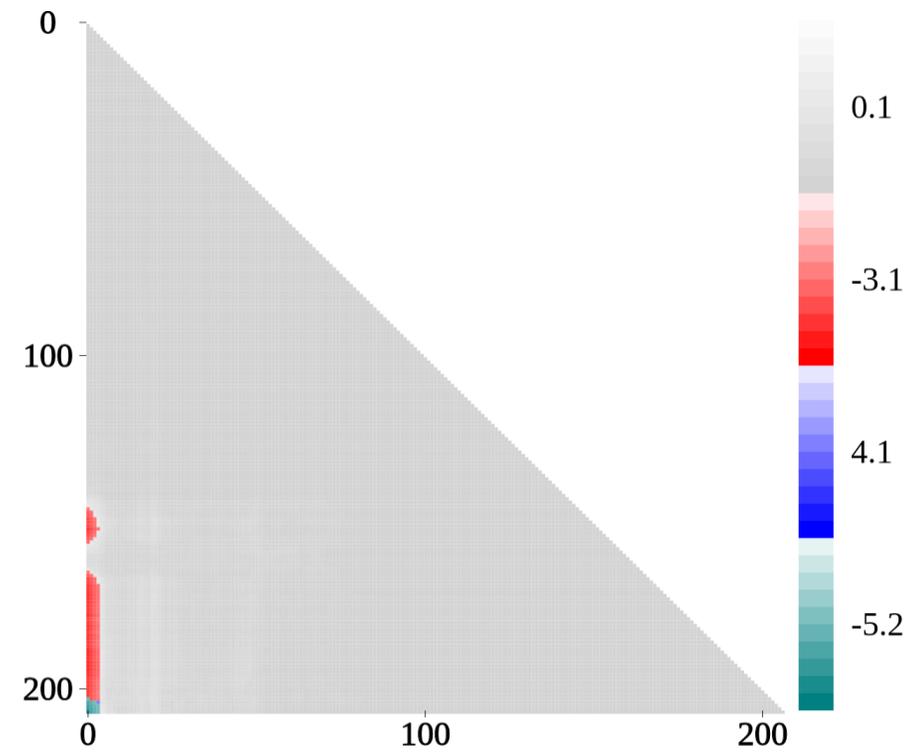


Protein UCH-L1

Proportion method

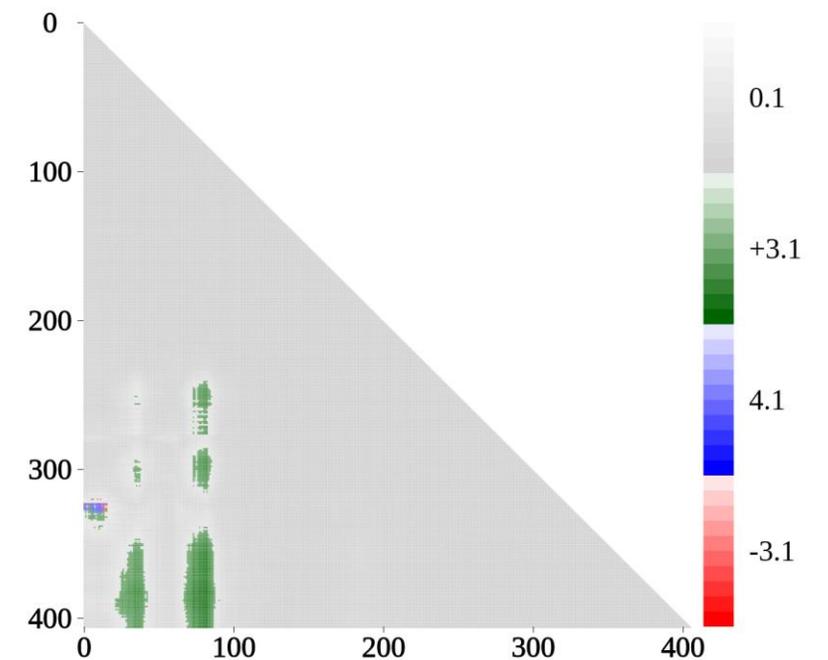
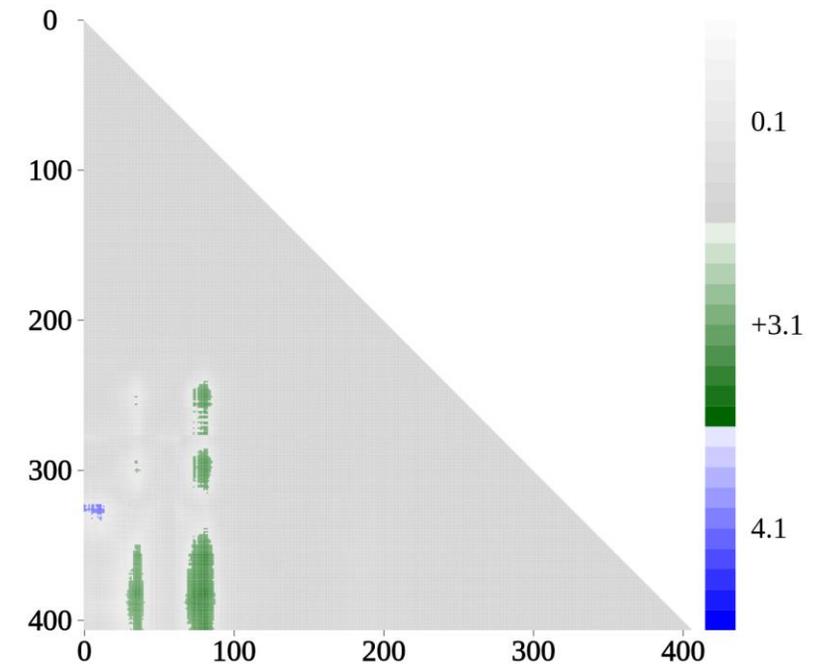


Accumulation method



What these graphs tell us

- What kind of knotting is happening at what location
- New knot types appear with accumulation method
- Frequent knotting locations
 - Grouping near axis
 - Center spot



Future Work

- Do this for all proteins and compare/contrast
- Develop a more complex "family tree" of relationships between knot types so we can better group the data for our accumulations

Acknowledgments

- Dr. Eric Rawdon
- Addie McCurdy
- Brandon Tran
- University of St. Thomas, St. Paul
- National Science Foundation
- KnotProt database
- KnotPlot

Thank you!