Protein Knots

a tangled story

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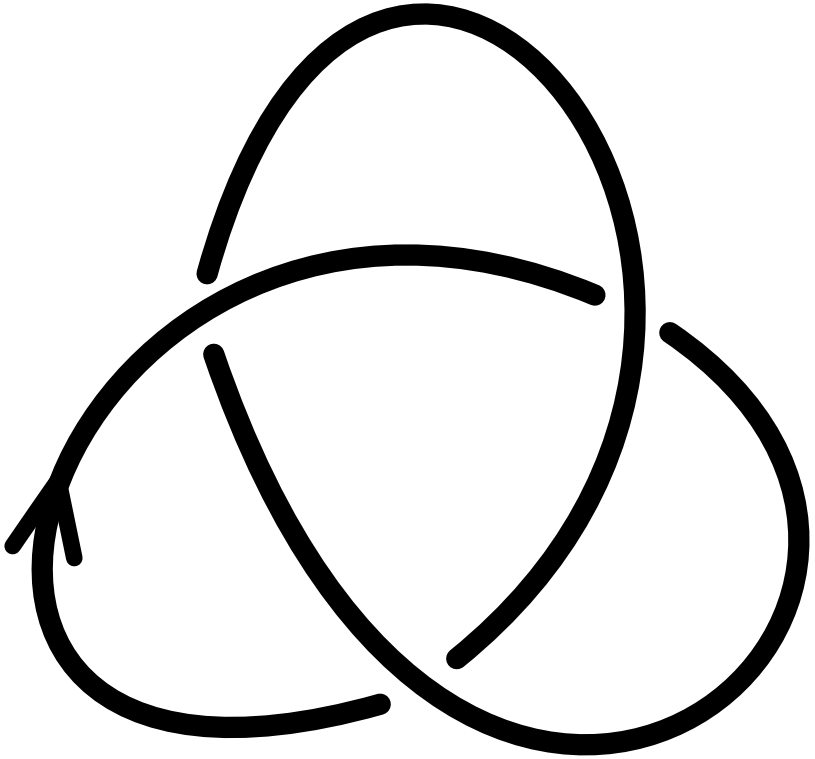
Knots

- Be it shoelaces or ropes, we find knots in our everyday life.
- *“a loop in a string which tightens when pulled”*
- Characterized by *knot invariants*.

Mathematically,

A knot requires its ends to be joined so that it cannot be undone. It is also referred to as the *closure* property.

Examples



Trefoil Knot

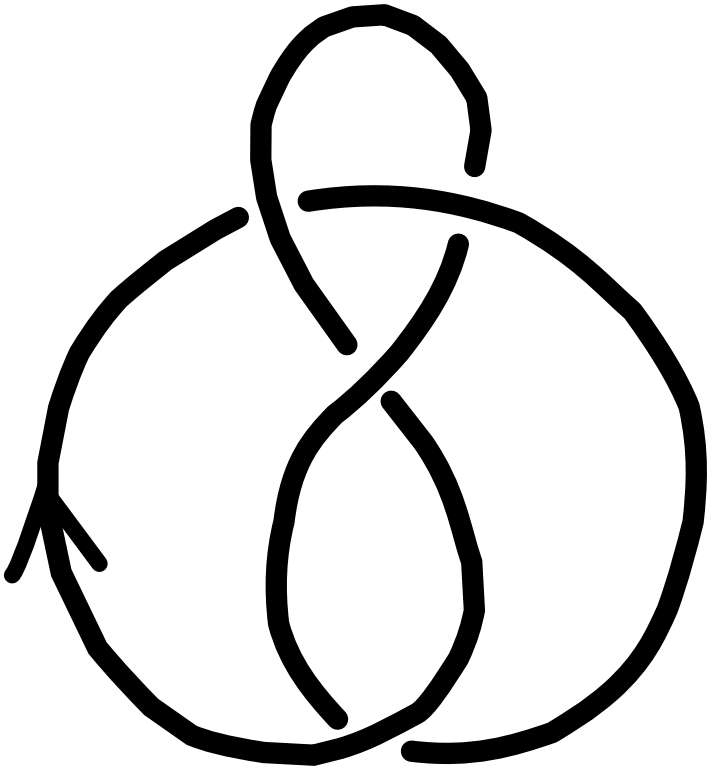


Figure of eight knot

Knots and biology

- DNA is often circular (closed curve!) and highly intertwined, knotted and coiled.
- *topoisomerase* and *recombinase* can change the topology of the DNA molecule in various ways.
- Knot theory has been successfully applied to DNA knotting and recombination process.
- Provides a quantitative, powerful, and invariant way to measure properties of DNA.

Knots in proteins?

But proteins aren't closed! The ambiguity in a protein knot definition arises due to several reasons.

- How do we detect *non-trivial* knots?
- How do we detect the knot type?
- What about the cross links?

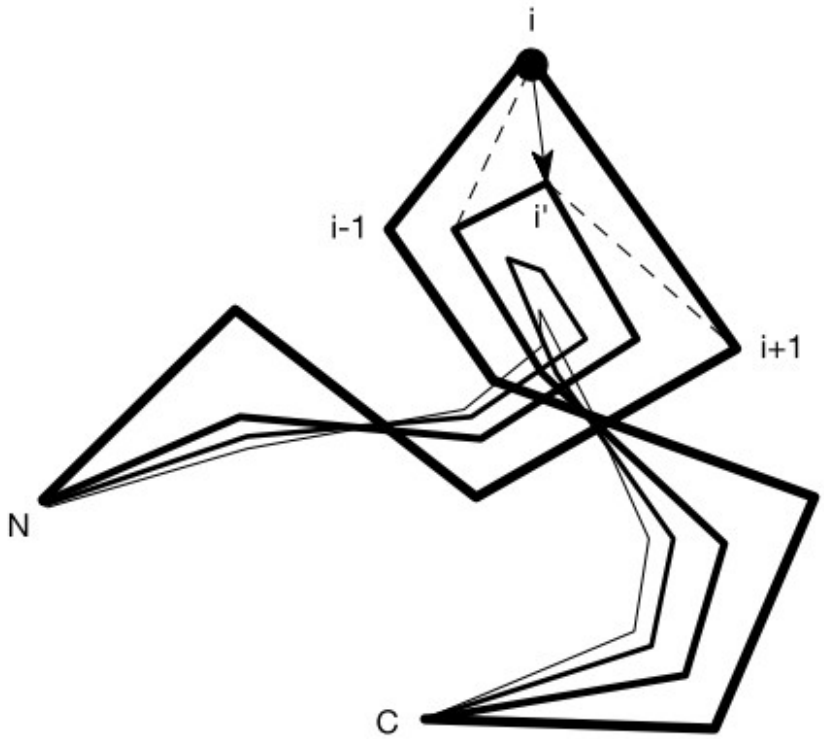
Detecting knots: Two ways

- Hold the ends fixed and deform the backbone. And then interpret the final configuration.
- Start with an open knot and complete it to a topological knot and then identify the knot type.

Both approaches involve simplifying structures using *Knot diagrams.*

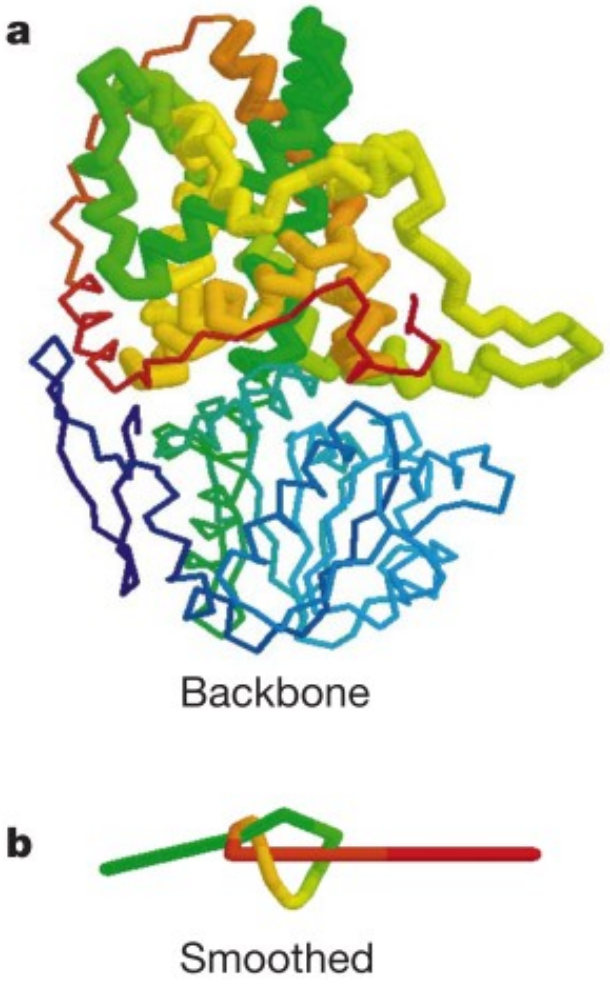
Detecting knots: First method

Hold the ends fixed and deform the backbone. And interpret the final configuration

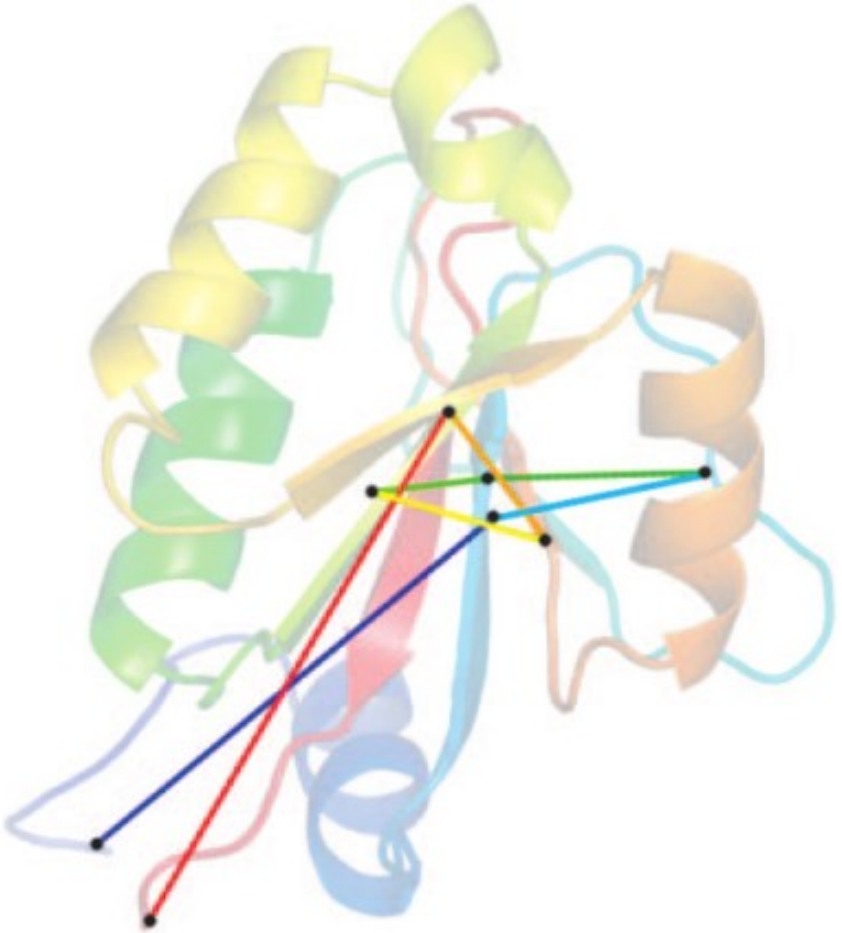


- KMT algorithm
- Knotfind algorithm

Examples



KMT algorithm



Knotfind algorithm

Detecting knots: Second method

Start with an open knot and complete it to a topological knot.

- Calculating knot invariants like *Alexander polynomial* or *Jones polynomial*

Trefoil knot

$$\Delta_k(x) = (1/x) - 1 + x$$

Figure eight knot

$$\Delta_k(x) = -(1/x) + 3 - x$$

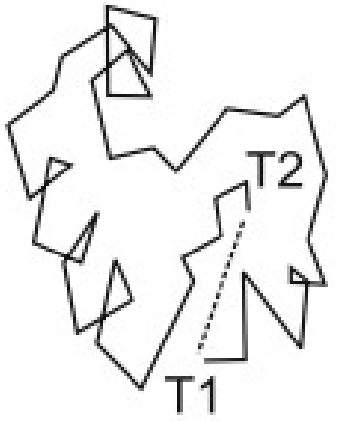
Unknot*

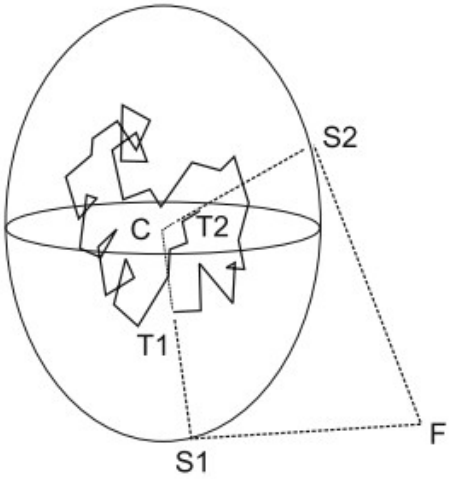
$$\Delta_k(x) = 1$$

Creating a closure

Several approaches:

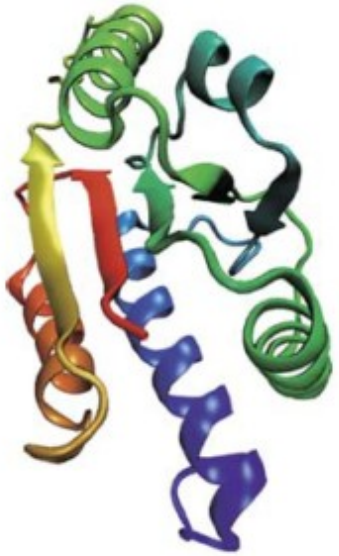
- Direct N-C join
- Center closure
- Random closure



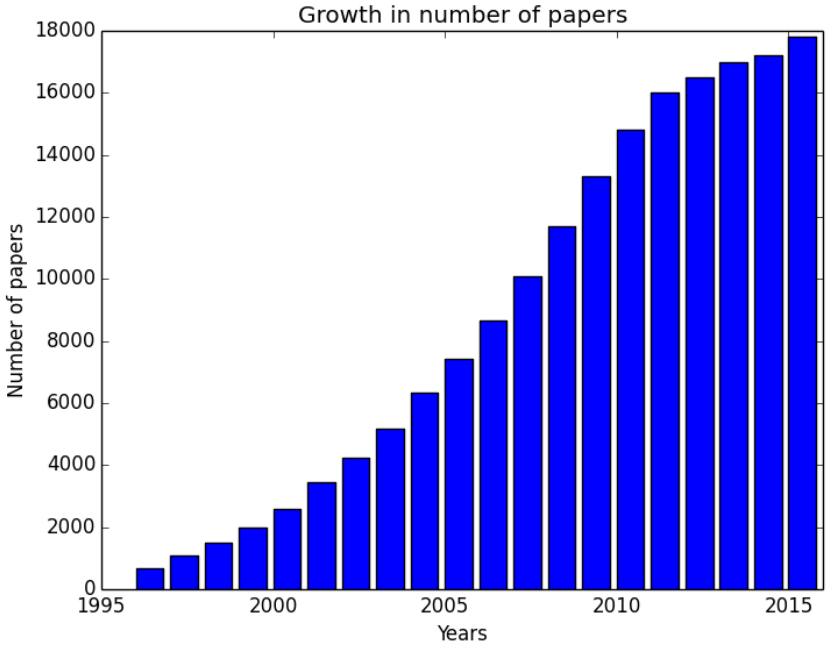


Identifying knots

- Reduce the number of crossings and inspect visually.
- Use calculators which determine knot invariants.



Interest in topic



Knots (1994): 1

Knots (2015): 900+

Source: Google Scholar,
KnotProt database
(http://knotprot.cent.uw.edu.pl/)

Types

- Shallow and Deep knots
- Trefoil knot (3_1)

  RNA methyltransferases, SAM synthetase
- Figure-of-eight knot (4_1)

  acetohydroxy acid isomeroreductase
- Five-crossing knot (5_2)

  ubiquitin hydrolase

Open questions

- Do knots provide extra physiological stability to protein structure?
- Why are knots so under-represented in protein population (~1% of total population)?
- How does a knotted protein fold?
- Why and how do they occur?

Potential answers

- Knotted proteins might exist as knotted molecules in their unfolded state
- Knots provide stability, resistance to cellular translocation and degradation pathway.

Future

- Figuring out a sequence pattern and map it to related function.
- Improve our understanding of folding pathway
- Investigate benefits of knots.
- If possible, given a knot K, to build a protein backbone with that knot

References

Mansfield (1994, 1997)

Khatib et. al. (2006)

Taylor et. al. (2000, 2002)

Mishra et. al. (2012)

Thank you!

Questions!