Using self-avoiding polygons
to study DNA-enzyme interactions

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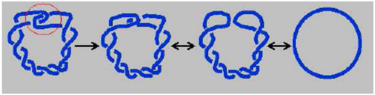
Motivation for this work

- DNA is highly compacted and self-entangled in the nucleus of a cell. Knotting interferes with cell functions such as replication.
- In order for DNA to be replicated, it needs to be first unknotted and unwound and near the end of the replication process, the mother and daughter strands of DNA need to be unlinked. Nature's solution to these entanglement and linking problems is a group of enzymes referred to as topoisomerases.



http://www.math.fsu.edu/~jmann/KnotOnMtn.htm

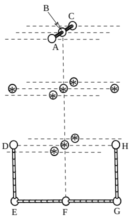
- During the replication process, topoisomerases locally interact with DNA to efficiently unknot and unlink the DNA but these are global properties.
- How a topoisomerase identifies the site at which it acts is an open question in Molecular Biology; the answer is of extreme importance in the treatment of cancer.

Motivation (cont'd)

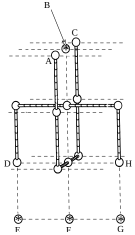
- A current cancer treatment, topo-inhibitors, may be administered to a patient with cancer.
- The inhibitor effectively prevents topo from acting in the replication process of all cells.
- The results of which are both positive and negative.
- The work presented here is motivated by trying to better understand these DNA-topoisomerase interactions.

Modelling a "Pinched" Ring Polymer

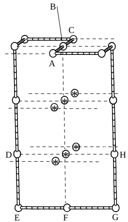
- Assume two strands of the ring polymer have been brought close together
- To model this pinched portion of a polymer, use the Local Strand Passage (LSP) model from Szafron and Soteros 2011.
- SAPs will be required to contain the fixed structure Θ (Θ-SAPs)
- A strand passage in a Θ-SAP can be modelled by replacing Θ with the structure Θ_s provided the necessary vertices are not occupied.
- If the vertices necessary for a successful strand passage are not occupied in a Θ-SAP, the SAP is referred to as a successful strand passage polygon; otherwise the Θ-SAP is referred to as a failed strand passage polygon.

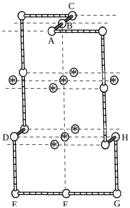


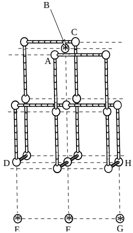
Θ



Θ_s







Counting SAPs

- If the vertices necessary for a successful strand passage are not occupied in a SAP containing Θ, the SAP is referred to as a successful strand passage polygon; otherwise the SAP is referred to as a failed strand passage polygon.
- $p_n^{\Theta}(K)$ is the number of distinct n-edge knot-type K SAPs in $\mathbb{Z}^3$ that contain Θ in the class formed by connecting vertex A to vertex H and vertex C to vertex D.
- For the moment we are going to focus on $p_n^{\Theta}(\phi)$.

Some background

- p_n is the number of distinct n-edge SAPs in $\mathbb{Z}^3$; Hammersley (1953) proved p_n grows that the exponential rate given by

$$\kappa := \lim_{n\to\infty} \frac{\log p_n}{n}.$$

- Sumners and Whittington [9] proved the Frisch-Wasserman Delbruck Conjecture: Sufficiently long rings polymers will be knotted with high probability, for the set of self-avoiding-polygons (SAPs) in $\mathbb{Z}^3$; More specifically,
  - $p_n(\phi)$ is the number of distinct unknotted n-edge SAPs in $\mathbb{Z}^3$
  - Sumners and Whittington [9] proved, as $n \to \infty$,

    (1) $1 - \frac{p_n(\phi)}{p_n} \to 1$ exponentially.

    (2) $\kappa_\phi := \lim_{n\to\infty} \frac{\log p_n(\phi)}{n}$ exists (Sumners and Whittington [9]); hence $p_n(\phi)$ grows at the exponential rate $\kappa_\phi < \kappa$.
- Question: At what rate does $p_n^{\Theta}(\phi)$ grow?

Growth Rate for $p_n^{\Theta}(\phi)$

- To establish the growth rate:
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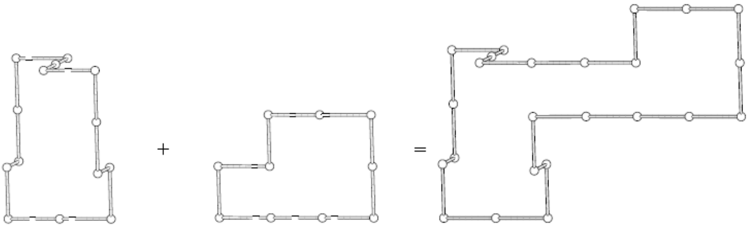
  - To determine a lower boundary for $p_n^{\Theta}(\phi)$: Consider a 14-edge Θ-SAP and an $(n-14)$-edge unknotted SAP.



Growth Rate for $p_n^{\Theta}(\phi)$

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- Combining these two inequalities, applying logarithms, dividing by n, and taking the limit through even n yields

$$\lim_{n\to\infty} \frac{\log[(1/2)p_{n-14}(\phi)]}{n} \leq \lim_{n\to\infty} \frac{\log p_n^{\Theta}(\phi)}{n} \leq \lim_{n\to\infty} \frac{\log np_n(\phi)}{n}$$

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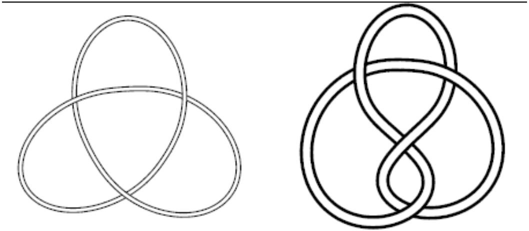
- In other words, $p_n^{\Theta}(\phi)$ grows at the same exponential rate κ_ϕ as $p_n(\phi)$.

Growth Rate for Non-trivial Knot-types

- Suppose we are interested in the growth rate of $p_n^{\Theta}(K)$, the number of n-edge non-trivial knot-type K Θ-SAPs. For example, K might be a trefoil (left) or figure eight (right) as illustrated below.



Growth Rates (cont'd)

- Open Question: Does the limit

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- Soteros, Sumners, and Whittington (1992) proved

$$\lim\inf_{n\to\infty} \frac{\log p_n(K)}{n} \leq \lim\sup_{n\to\infty} \frac{\log p_n(K)}{n} < \kappa.$$

Back to Modelling Topoisomerases

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- A commonly asked question regarding the Θ-SAP model for a strand-passage induced by a topoisomerase:
- “The Θ-SAP model is a very simplistic model. Is such a simple model able to capture any properties of a topo-DNA interaction actually observed by molecular biologists?"
- The answer is ...

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- In Neuman et al (2009), the authors consider the angle formed by the two DNA strands at the site at which a topo acts. They show that the angle, on average, at the strand passage site is approximately 85^o.

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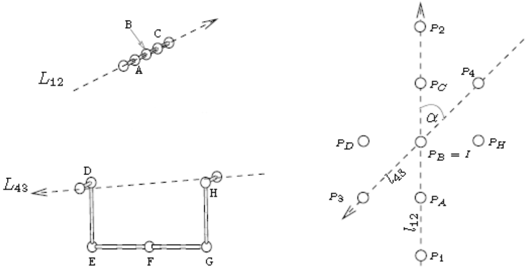
- Using our Θ-SAP model, we can form a "crossing angle" as follows:



(a) (b)

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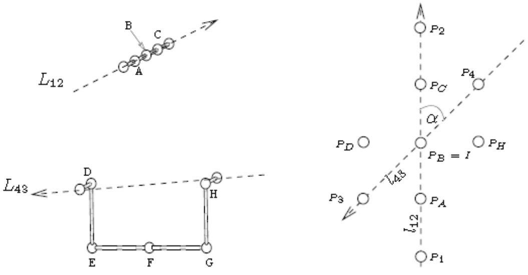
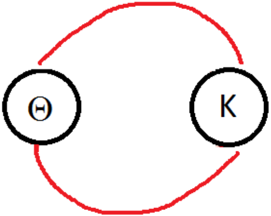


(a) (b)

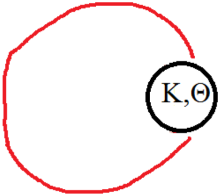
- In Szafron and Soteros (2011) we provide numerical evidence that if a strand passage occurs at a site with an acute crossing angle, then the strand passage is more likely to unknot a knot then knot an unknot.

Preliminary Work

- Two cases:
  - Case 1: Θ is not part of the knotted portion

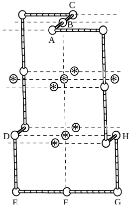


  - Case 2: Θ is part of the knotted portion



Preliminary Work (cont'd)

- A Θ-SAP can be decomposed into Θ and two undirected self-avoiding walks (uSAWs).



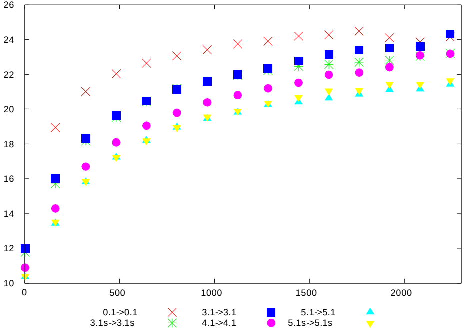
- $\mathcal{E}_n(K)$ is the set of "*equal-sided* Θ*-SAPs*" in $\mathcal{P}_n^{\Theta}(K)$ and $\mathcal{E}_n^c(K)$ is the set of "*unequal-sided* Θ*-SAPs*" in $\mathcal{P}_n^{\Theta}(K)$.
- If $K = \phi, \kappa_\phi := \lim_{n\to\infty} \frac{\log |\mathcal{E}_n^c(\phi)|}{n} = \lim_{n\to\infty} \frac{\log |\mathcal{E}_n(\phi)|}{n}$.

Preliminary Work (cont'd)

- For $\omega \in \mathcal{E}_n^c(K)$, let $\mathfrak{w}_s(\omega)$ and $\mathfrak{w}_l(\omega)$ respectively be the smaller and larger of these uSAWs of ω.
- Marcone et al (2005, 2007) present a measure for the size of a knot, and they conjecture that, according to their measure, that the knot is weakly localized (ie the average length grows like n^t for $0 < t < 1$). Their numerics support $t = 0.75$ for knot-types $3_1, 4_1, 5_1$.
- We are going to focus on the small uSAW.
- How does the length of $\mathfrak{w}_s(\omega)$, on average, grow as a function of the length of ω?

The Length for Case 1

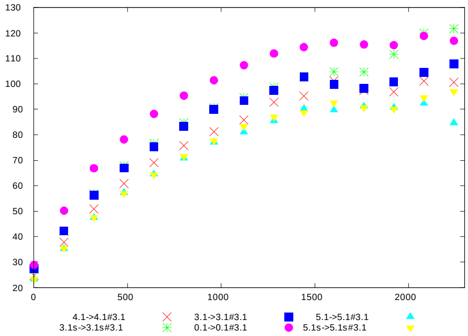
- $\langle |\mathfrak{w}_s(\omega)| : K \to K\#\phi) \rangle$ versus N



	t	95% ME
0_1->0_1#0_1	0.084	0.032
3_1->3_1#0_1	0.148	0.011
3_1s->3_1s#0_1	0.136	0.016
4_1->4_1#0_1	0.173	0.011
5_1->5_1#0_1	0.168	0.016
5_1s->5_1s#0_1	0.171	0.014

The Length for Case 1 (cont'd)

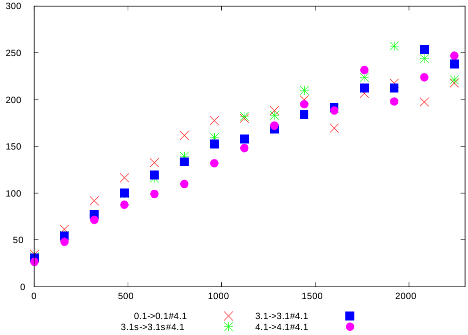
- $\langle |\mathfrak{w}_s(\omega)| : K \to K\#3_1 \rangle$ versus N



	t	95% ME
0_1->0_1#3_1	0.325	0.034
3_1->3_1#3_1	0.384	0.022
3_1s->3_1s#3_1	0.327	0.052
4_1->4_1#3_1	0.376	0.034
5_1->5_1#3_1	0.35	0.052
5_1s->5_1s#3_1	0.382	0.031

The Length for Case 1 (cont'd)

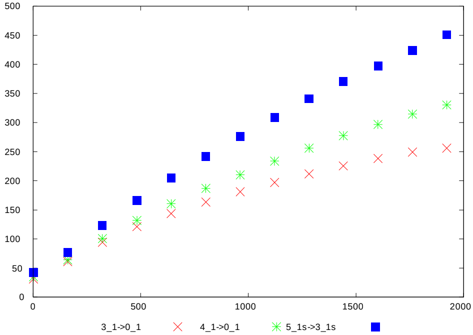
- $\langle |\mathfrak{w}_s(\omega)| : K \rightarrow K\#4_1) \rangle$ versus N



	t	95% ME
0_1->0_1#4_1	0.487	0.072
3_1->3_1#4_1	0.578	0.024
3_1s->3_1s#4_	0.578	0.052
4_1->4_1#4_1	0.639	0.048

The Length for Case 2

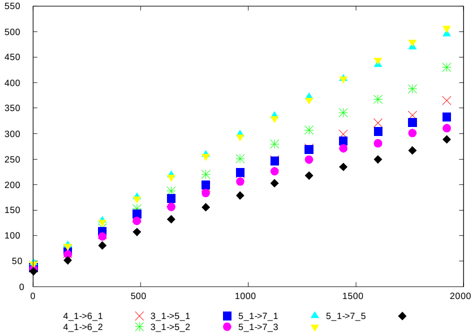
- $\langle |\mathfrak{w}_s(\omega)| : K \to K\prime \rangle$ versus N



	t	95% ME
3_1->0_1	0.572	0.007
4_1->0_1	0.665	0.003
5_1s->3_1s	0.721	0.003

The Length for Case 2

- $\langle|\mathfrak{w}_s(\omega)| : K \to K\prime)\rangle$ versus N



Conclusions

- Understanding the behaviour of these small walks is an ongoing work.
- Using Θ-SAPs to study DNA-enzyme interactions is a good starting place.
- Using a lattice model allows you rigourously prove things.
- Thank you.

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