

Progress Report

Modeling the mechanism of topoisomerase

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1. Goals
2. Literature Review
3. Initial Ideas

Goals



Overall goal

- Understand the interaction of *TOP2* and the topology of DNA.

This week goal

- Review Matlab programming.
- Understand the dynamics and fluid-coupled system of DNA.
- (Hopefully) Start to model.

Literature Review

Linking number

$$Lk(C_1, C_2) = \frac{1}{4\pi} \oint_{C_1} \oint_{C_2} \frac{\mathbf{x}'_1(s_1) \times \mathbf{x}'_2(s_2) \cdot [\mathbf{x}_1(s_1) - \mathbf{x}_2(s_2)]}{|\mathbf{x}_1(s_1) - \mathbf{x}_2(s_2)|^3} ds_2 ds_1$$

Writhe

$$Wr(C) = \frac{1}{4\pi} \oint_C \oint_C \frac{\mathbf{x}'(s_1) \times \mathbf{x}'(s_2) \cdot [\mathbf{x}(s_1) - \mathbf{x}(s_2)]}{|\mathbf{x}(s_1) - \mathbf{x}(s_2)|^3} ds_2 ds_1$$

Twist

$$Tw(C_2, C_1) = Lk(C_1, C_2) - Wr(C_1)$$

Simplified Model (Swigon, 2009)

Elastic Energy

$$\Psi = \frac{1}{2} \int_0^L \overbrace{A |\mathbf{t}'|^2}^{\text{bending}} + C \underbrace{\left([\mathbf{t}_1 \times \mathbf{d}] \cdot \mathbf{d}'(s) - \bar{\Omega} \right)^2}_{\text{squared difference of twist density}} ds \implies A (\mathbf{t} \times \mathbf{t}'') + C \Delta \Omega \mathbf{t}' = \mathbf{F} \times \mathbf{t}$$

Under standard condition: $A \approx 50kT \cdot \text{nm}$, $C \in [25, 100]kT \cdot \text{nm}$

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Electrostatic Energy

For M charged sites,

$$\Phi = \frac{4\delta^2}{4\pi\epsilon} \sum_{m=1}^{M-1} \sum_{n=m+1}^M \frac{\exp(-\kappa |\mathbf{x}_m - \mathbf{x}_n|)}{|\mathbf{x}_m - \mathbf{x}_n|}$$

Generalized Kirchhoff's Rod Dynamics

$$\partial_t \mathbf{P} = \mathbf{F}' + \mathbf{f} \quad \text{(linear momentum)}$$

$$\partial_t \mathbf{R} = \mathbf{M}' + \mathbf{x}' \times \mathbf{F} + \mathbf{m} \quad \text{(angular momentum)}$$

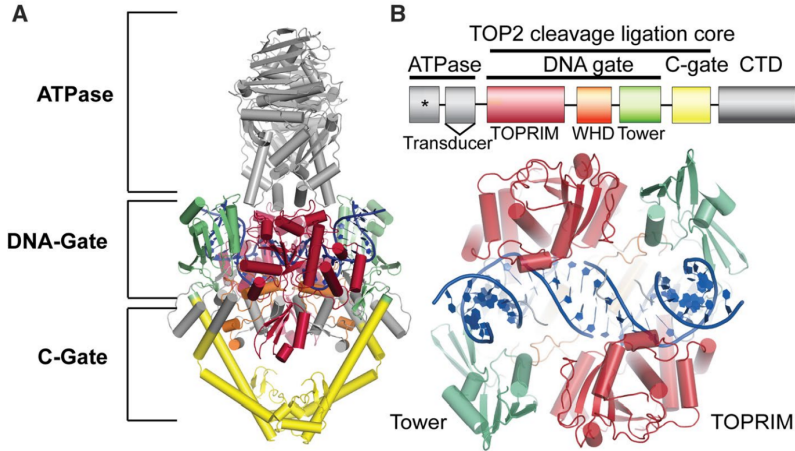


Figure 1: *TOP2* Schematic on *S. cerevisiae* (Riccio *et al.*, 2020)

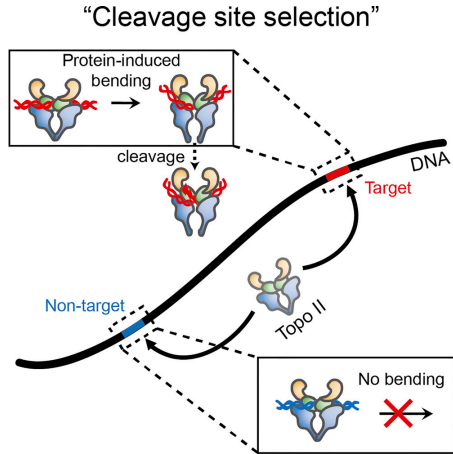


Figure 2: Possible mechanism of identifying cleavage site (Jang *et al.*, 2019)

Initial Ideas



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Naive Ideas (con't)

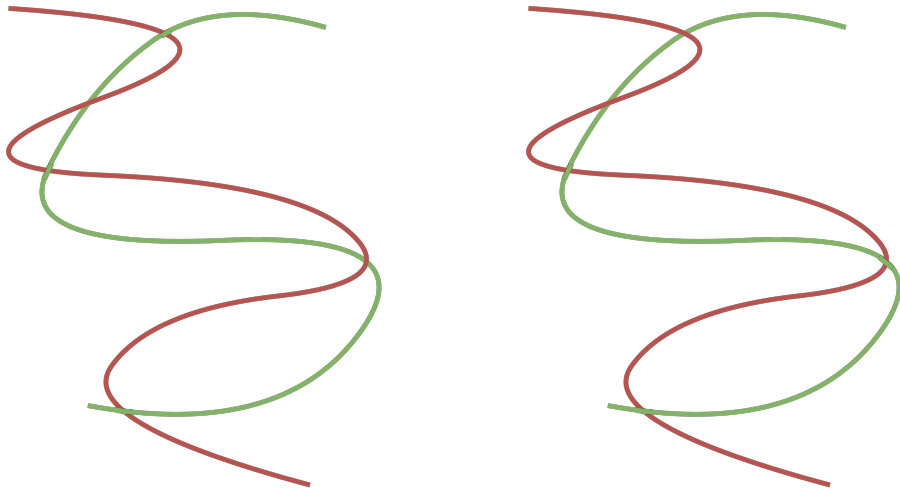




Figure 3: Visualize the process. Left side is original and right side is randomly transformed

-  JANG, Y., SON, H., LEE, S.-W., HWANG, W., JUNG, S.-R., BYL, J. A. W., OSHEROFF, N., AND LEE, S.
Selection of dna cleavage sites by topoisomerase ii results from enzyme-induced flexibility of dna.
Cell Chemical Biology 26, 4 (2019), 502–511.e3.
-  RICCIO, A. A., SCHELLENBERG, M. J., AND WILLIAMS, R. S.
Molecular mechanisms of topoisomerase 2 dna–protein crosslink resolution.
Cellular and Molecular Life Sciences 77, 1 (Jan 2020), 81–91.



SWIGON, D.

The mathematics of dna structure, mechanics, and dynamics.

In *Mathematics of DNA Structure, Function and Interactions* (New York, NY, 2009), C. J. Benham, S. Harvey, W. K. Olson, D. W. Sumners, and D. Swigon, Eds., Springer New York, pp. 293–320.