The Crossroads of Topology, Combinatorics and Biosciences: Deciphering the Entanglement of Multi-stranded Nucleic Acids

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1 Overview of the Field

The nucleic acids DNA and RNA encode the genetic code of living organisms and of viruses. They typically occur in the form of long polymers that are subjected to high levels of confinement. In living cells, nucleic acids are substrates of important cellular processes such as replication, recombination and transcription. Nucleic acids also provide prime materials for a bottom-up construction of three-dimensional (3D) systems to the highest possible, nano level, precision. Both the biological processes and the nanostructure constructions alter the geometry and topology of DNA and RNA and can induce the formation of multi-stranded or hybrid structures. *Characterizing the geometry and topology of multi-stranded nucleic acids is at the heart of understanding fundamental biochemical mechanisms.* In this regard, there are several prominent open questions which were the focus of this workshop.

Topology of RNA and DNA: DNA molecules display different levels of entanglement within their natural environment. For example, DNA coils and knots as it packages in bacteriophage capsids [Arsuaga2005, Cruz2020, Hiltner2021]. DNA supercoiling and other forms of entanglement can affect biological processes such as DNA recombination, replication and transcription [Chédin2020, Pouokam2019, Shimokawa2013]. Tools from low-dimensional topology shed deep insight on the action of recombination enzymes (e.g. [Stolz2017, Lidman2019, Moore2020]). Likewise, the experimental and computational study of circular DNA molecules provides valuable information on the topology of DNA plasmids and extrachromosomal circular DNA [Fogg2021, Irobalieva2015, Shoura2017]. Relatedly, the three-dimensional structure of RNA encodes functional information [Shapiro2007], and therefore understanding the spatial embedding into which an RNA molecule co-transcriptionally folds is a problem of key importance in molecular biology.

Topology of RNA-DNA hybrids: There is a rapidly growing interest in the study of RNA-DNA hybrids known as R-loops. R-loops are three-stranded structures formed during transcription when the nascent RNA re-anneals with its template DNA, leaving an unbound coding single stranded DNA. Although traditionally considered as a threat to genome integrity, recent studies suggest that R-loops also play regulatory roles in cellular processes [Hegazy2020]. As such, it is critical to unravel the driving factors underpinning R-loop

formation and stability. In [Stolz2019], the authors combined modeling and experimental work, and showed that both DNA sequence and topology influence R-loop formation. Yet, little is understood about their topological entanglement. For example: Does the free coding DNA wrap around the RNA-DNA complex? Or does it fold upon itself to form a complex 3D structure? [Carrasco-Salas2019]. In [Jonoska2021] the authors proposed a grammar model for studying R-loop formation.

Topology of DNA and RNA within nanostructures: The informational character of the DNA and RNA bases and their Watson-Crick complementarity guide the construction of novel nanostructures through bottom-up self-organization [Benson2015, Geary2014, Geary2021, Rothemund2006, Song2017]. In general, there are no mathematical descriptions of the topologies of the strands forming these structures. For example, the unit building blocks originally used to form a 3D DNA crystal are tensegrity triangles that are built of seven DNA strands [Zheng2009]. These units have recently been experimentally twisted from right handed duplex crossings into left handed, and are capable of providing very rich topological knotting once they assemble into 3D crystals. However, we lack the mathematical methods needed for predicting the variety of topological structures that result from changes in the units [Woloszyn2022].

2 Recent Developments and Open Problems

Complex biological systems are generally studied using differential equations, dynamical systems, and statistical analysis. Over the last four decades, techniques from low-dimensional topology and combinatorics have proven to be successful and versatile for studying the entanglement of nucleic acids and their interactions with enzymes. Knot theory is the study of simple closed curves that can be manipulated via continuous maps. Biopolymers can be open or closed and can form knots, links and self-intersecting networks. Understanding the entanglement of biopolymers is of interest in various fields. An emerging body of work applies knot theory to examine the topology and geometry of biopolymers [Arsuaga2005, Panagiotou2019, Pouokam2019, Shimokawa2013, Stolz2017, Moore2020]. Quantitative studies of entanglement complexity provide insights into the function of biopolymers and the biological processes that involve them [Hiltner2021, Irobalieva2015, Panagiotou2019, Pouokam2019, Stolz2019]. Combinatorics, on the other hand, deals with properties of finite, or countably infinite, objects. By their nature, biopolymers like DNA and RNA are amenable to combinatorial modeling and analysis. Methods based on words over finite alphabets, formal languages, and graph theory have been developed to address questions about interactions and structures of nucleic acids, opening the door to discrete methods for data analysis [Bonvicini2020, Burns2016, Ellis-Monaghan2019, Heitsch2014]. Importantly, works such as [Angeleska2009, Jonoska2021, Mohammed2020] bridge applied knot theory, topological graph theory and applied combinatorics by blending ideas from these fields, thus highlighting the benefits of exploring integrated approaches to inspect biomolecular processes. Applied knot theory and applied combinatorics have also been blended to characterize polymer entanglements using lattice models of polymers under confinement [Beaton2018, Beaton2022], leaving open the door for integration with other combinatorial approaches.

Addressing the open geometry and topology questions regarding multi-stranded nucleic acids poses a wide variety of mathematical, computational and experimental challenges. Methods arising from combinatorics, (topological) graph theory, knot theory and low-dimensional topology are essential to making progress on those questions. Interactions amongst mathematicians, polymer modelers and experimentalists are critical. The workshop *The Crossroads of Topology, Combinatorics and Biosciences: Deciphering the Entanglement of Multi-stranded Nucleic Acids* connected researchers working in overlapping areas who do not normally interact and maximized their interactions.

This workshop revolved around the following themes:

- **Applied Knot Theory**: Analytical and computational tools for modeling biopolymers, measuring their entanglement complexity, and the action of enzymes that act on them. The asymptotic behavior of these methods.
- **Applied Combinatorics and Graph Theory**: Topological graph theory and studies of mesh and complex 3D embeddings to examine interactions of DNA and/or RNA strands as well as the resulting

spatial molecular arrangements. Data analysis approaches leveraging those tools.

- **Structural Biochemistry**: Modern experimental methods and results to probe nucleic acid entanglement under different topological conditions of the nucleic acid substrates, including R-loop formation, RNA and DNA foldings and multi-strand embeddings.

3 Presentation Highlights

Workshop organization and diversity of the participants

The workshop included 5 one-hour talks given by five researchers from different areas of expertise: a mathematician, a mathematical molecular biologist, a physicist, a chemist and a molecular biologist. The long talks introduced various aspects of nucleic acid structures and modelling. These introductory presentations were accompanied by 22 specialized 30-minute presentations. We had two working group periods (Tuesday and Thursday) when the participants were separated into smaller subgroups for specialized discussions. Two evenings were dedicated to special events, one being a panel/open discussion addressing issues that researchers at all levels may be facing with regard to "keeping their research in STEM alive", and the other being a special software presentation on KnotPlot [KnotPlot]. On Tuesday afternoon we had a special poster session with 5 posters that remained in the lobby until the end of the week. The workshop was organized by four female mathematicians at different career stages. The overall on-site participation of women was about 50%. In addition participants came from diverse racial and ethnic backgrounds. Diversity was further increased by encouraging and facilitating online participation for those who due to illness, caregiving responsibilites or financial constraints could not attend in person.

3.1 Nucleic Acid Nanostructures

Nucleic acid nanostructure presentations focused on nucleic acid biotechnology and contained recent experimental results and theoretical approaches. S. Vecchionni discussed advances in research about DNA crystallographic structures and the different building blocks that serve as units in the crystals. These units have also chirality that is imposed by the length of the edges of the units and they exhibit different rhombohedral and hexagonal crystallographic structures. C. Geary discussed advances in RNA origami, that is structures built by co-transcriptional RNA folding. These structures have the advantage of being built *in vivo* by inserting the desired DNA sequence within a genome.

Both of these experimental talks were accompanied by talks on mathematical developments on problems arising from the experimental data. Since the crystallographic structures have no proper mathematical framework, M. Saito and E. Panagiotou proposed in their talks approaches for developing mathematical invariants that are based on knotoids and linkoids. E. Panagiotou proposed extensions of the Gauss linking number. M. Saito proposed 2D and 3D tiling approaches to classify crystallographic groups as well as subgroups that preserve components, indicated by the same strand connections within the structures.

Spatial graphs appear as models in protein bonds as well as in DNA mesh structures. The presentation by L. Kauffmann focused on 4-valent rigid vertex graphs with applications to protein folding. J. Ellis-Monaghan discussed DNA scaffold strand routing (Eulerian graphs with A- and O-trails) with application to 3D DNA graph assemblies.

P. Rainford's approach was to develop genome design and coding that would induce topological supercoiling on the DNA molecule and be used as a gene regulatory mechanism. As such, this process would be a starting point for a general logic gate and circuit design.

3.2 DNA Topology and Enzymatic Activity

DNA topology presentations included novel experimental results and novel topological or numerical approaches for modelling DNA in solution. L. Zechiedrich presented experimental work showing that DNA supercoiling, looping and counterions are important towards controlling access to the primary code carried by the base pair sequence of DNA. The presentation highlighted how site-specific base pair disruptions (base flips) facilitate very sharp bends in DNA even at distant sites and argued that, to understand the role of

counterions such as Calcium in bioprocesses, models need to be less protein-centric and must consider the secondary structure of DNA. [Irobalieva2015, Fogg2021]

M. Gamill showed atomic force microscopy (AFM) images of DNA knots. He presented a new open-source software, TopoStats, that enables single molecule determination of DNA topology from raw AFM images. The resolution achieved by AFM at DNA crossings enables the determination of crossing direction at each point and thus the explicit determination of topology. He described how the software works and exhibited its features. This tool provides a promising way to explore the role topology plays for DNA *in vitro* or *in vivo*. Audience members offered to provide samples of catenated mini-circles and RNA-DNA hybrids for AFM analysis. [Provan, Beton2021].

C. Prévost, a computational biologist who works closely with experimentalists, discussed her study of the interweaving of DNA strands in homologous recombination. Homologous recombination catalyzes the faithful repair of DNA double strand breaks (DSB). She presented Molecular Dynamics results for different stages of the process and highlighted the role of base flips and the local stretching and unwinding of the DNA. [Prentiss2015, Yang2015, Boyer2019, Danilowicz2017, Danilowicz2021].

On the topology side, K. Shimokawa discussed the methods for determining unlinking pathways of DNA catenanes. Site-specific recombination is modeled by using band surgeries on knots and links. Characterization of shortest pathways and their mechanisms were discussed. The key idea is in establishing the relationship between two knot invariants, such as crossing numbers and signatures. [Shimokawa2013, Stolz2017, Ishihara]

M. Schmirler presented a new simple cubic lattice model with ionic interactions to represent DNA in salt solution. His model includes bending rigidity and long range DNA interactions and uses stochastic approximation methods to fit to the DNA knotting experiments performed by [Shaw1993, Rybenkov1993]. The persistence length measured from the resulting model is comparable to DNA and predictions for how knotting probability increases with DNA length are comparable to results for a discrete worm-like chain model.

A. Rechnitzer presented a new topology-preserving algorithm for equilateral random polygons in 3-space. The Markov Chain Monte Carlo algorithm is based on 2-point pivot moves, where moves are further restricted to prevent strand passages and hence preserve topology. The efficiency of the algorithm is comparable to the approach of J. Cantarella if restricted to fixed topology sampling. While the Cantarella algorithm yields independent samples, the approach is slowed since knot identification is required to determine topology. Topology preserving algorithms allow for exploration of the configurations for more complex knots.

A. Pekoske Fulton presented an elastic model (Cosserat rod theory) with explicit solvent conditions to study DNA knots with high writhe. In this setting the writhe is induced by high salt concentrations. She presented two approaches, a deterministic generalized boundary method and a stochastic generalized boundary method. Using these methods she classifies minimal knotted conformations according to symmetries and identified a difference between the Gibbs distribution and the stationary distribution of highly supercoiled knots.

3.3 R-loops and RNA-DNA Hybrids

The study of R-loops was one of the focal points of the workshop (see introduction). Several presentations focused on various aspects of modeling R-loops. The opening presentation on this topic was given by S. Poznanović who showed a model based on formal grammars to study the formation of R-loops [Jonoska2021, Ferrari]. The model associates a separate symbol in the grammar to various stages of R-loop formation. Poznanović presented a probabilistic method (equivalent to a hidden Markov model) trained and tested on *in vitro* data and showed that this method improves results of models based on standard biophysics energy-based methods [Ferrari]. M. Riehl showed a model for R-loop formation based on sequence characteristics such as C-richness and CG-skewness. The model is based on accumulation of sequence-based parameters and specific threshold values that can be achieved as one varies the parameters [Jonoska2021].

Since the formation of R-loops depends on the ability of an RNA transcript to invade the template DNA duplex, Liu and colleagues hypothesize that features of the RNA secondary structure are predictors of R-loop formation [Liu]. P. Liu discussed an approach to predict R-loop formation using a tree representation of the secondary structure of the corresponding RNA transcript. He showed that tree representations can be completely characterized by polynomials. Considering the polynomials associated with experimental data,

Liu and colleagues determined that the sum of the polynomial coefficients are excellent predictors of R-loop formation. Furthermore, this model suggests that types of RNA secondary structures that contain multiple small bubbles without many branching loops are involved in R-loop formation [Liu].

C. Heitsch presented a combinatorial method to describe RNA secondary structures. She outlined a method to associate a set of trees representing RNA structures with a given nucleotide sequence. She also showed how these structures can be connected through certain tree operations that involve adding or removing branches.

R-loop structures can be modeled by θ-graphs. A. Moore presented new results in knot theory that generalize well-known mathematical results to θ-graphs (a special case of spatial graphs). A key difference between knots and spatial graphs is that the former are one-dimensional manifolds while a θ-graph is a 1-simplex (not a manifold). θ-curves are also connected to knotoids and are used to describe protein structure.

The presentation by E. Holleman focused on new *in vitro* experimental results on R-loops. In this work, Hollerman and colleagues designed 30 new plasmids that differ in a sequence of 200 nucleotides that is inserted near the start of a gene region. The nucleotide sequences of the insertions were designed to display desired characteristics (e.g. C-Richness, CG-skew, randomness etc..). Each plasmid construct was used as substrate for the R-loop formation experiments. The first set of experiments showed that nicked DNA promotes R-loop formation by lowering the energetic barrier at initiation and termination of the RNA-DNA hybrid. The second set of experiments tried to estimate the duration of the R-loops and the effect of the DNA/RNA branch migration process [Hollerman at al., in preparation]

3.4 DNA Packing and Genome Properties

Understanding DNA packing in bacteriophages and other viruses requires a better understanding of the molecular behavior within spatial restrictions. J. Arsuaga talked about the need to develop a new framework, both experimental and mathematical, to study DNA under confinement. Key aspects of DNA under confinement include DNA knotting and linking, the formation of liquid crystalline structures and a reevaluation of the importance of terms in the free energy equation, such as DNA bending, DNA electrostatics and DNA cholesterics. The mathematical analysis of these aspects combined models of random knotting with continuum models of liquid crystals. [Arsuaga2005, Liu2021] P. Pongtanapaisan talked about developing knot theory methods to study knots under tube confinement. The tube is used to model experimental data from nanochannels. He showed that the dimension of the tube that a knot can fit in, can be estimated from a colouring algorithm for knot diagrams.

New methods related to Hi-C experiments help to explore DNA nuclear packing and bending. M. Nicodemi presented advances in his and Pombo's "binders and string model" to analyze Hi-C data. The underlying premise of the work is that genes are heavily regulated by phase transitions that control chromosome folding. Under this model, molecular fine tuning is not necessary and gives more room for stochastic events. He discussed a new Hi-C implementation developed by himself and collaborators that aims at reducing biases introduced when more than two strands are trapped by the crosslinker in a Hi-C experiment. He showed applications and validation of the model to different regions of the genome such as EPHA4 gene in chromosome 2 and HoxB in chromosome 17. He also discussed how amplifications and deletions are reflected in the model and in the data, and the potential applications to genetic diseases. K. Ishihara and colleagues study distance maps arising form Hi-C experiments. A distance map is defined by considering the Euclidean distance between two points in a chain. If the chain is linked, Ishihara showed that the linking number can be calculated directly using the distance map. This method can be applied to studying interlinking of chromosomes.

M. Shoura talked about their methods developed to study extra chromosomal DNA (eccDNA). This is a phenomenon that takes place in cells through which sections of the genome are excised and kept as minicircles (independent of the rest of the genome). Circulome maps reveal hotspots of genome rearrangements and their localization. Shoura and colleagues have applied it to detect genomic erosion in cancer cell lines and proposed a mechanism for gene amplification in cancer. The talk presented experimental results and discussed bioinformatic methods for detecting the location of eccs.

F. Storici and L. Kari presented different views of 'packing' of nucleotides within the genome. F. Storici presented a study of ribonucleotide insertions in the mitochondrial human DNA. This is one of the unexpected genome irregularities that, according to her studies, may not be a random process, but there is a sequence

preference when these insertions appear. In particular, ribo C insertions happen more frequently than the other types of nucleotide insertions. Moreover, ribo insertions differ between the leading and the lagging strands in mitochondrial DNA. L. Kari showed a method that studies correlations within DNA sequences that help distinguish organisms and critical events that have influenced the structure of genomes. She combined this representation of the genome with machine learning to analyze signatures of organisms that live in extreme environments.

4 Scientific Progress Made

The main scientific progress was the identification of open problems of broad interest. We formed four research topic groups: DNA topology, DNA packing, R-loops and DNA/RNA nanostructures.

4.1 DNA Topology

The working group discussed questions on stability of supercoiling under different environmental conditions, enzymatic actions and chemical modifications. Experimental results show base flipping on negatively supercoiled plasmids; related to this, the group discussed the formation of non-standard DNA structures such as quadruplexes. Inspired by the action of topoisomerases, the group asked what are the interactions of other DNA binding proteins with supercoiled DNA. Knotting probability as a function of environmental ionic conditions was also discussed. In particular, it was noted that DNA knotting experiments, published in [Shaw1993, Rybenkov1993], contained very large concentrations of ions. This large concentration of ions may change DNA structure from B DNA to Z DNA or may introduce other effects that are not accounted for when modeling the data using the simple cubic lattice.

4.2 DNA Packing

Much is known about the theory of DNA in free solution at the atomistic level and at the macroscopic level. Challenges remain when trying to bridge between these scales and even more so when modelling DNA in confinement. The working group discussed that the liquid crystal framework is showing promise and considered whether a simplified lattice model might be useful. Related to that, it was suggested to add cholesteric interactions into a lattice model to see if the toroidal conformations identified experimentally could be observed. We also discussed the challenges of identifying knots and links from Cryo-Em images with many overlapping crossings - knot complexity grows with increased confinement - beyond the capabilities of the TopoStats software.

4.3 R-loops

Not much is known about the factors that control R-loop formation as well as their geometry and topology. Following S. Poznanović and E. Holleman's talks, the working group discussed how to expand the formal grammar model to study R-loop formation when a single strand break is introduced in the DNA. We also discussed whether the unpaired DNA strand in an R-loop is away or follows the groove of the RNA-DNA helix. AFM images show that the unpaired DNA strand is away from the duplex suggesting that if such a strand follows the groove then it is a transient structure. In addition, the working group discussed studies of sequence effects on DNA topology, such as `https://github.com/annareym/PLUMED_DNA-Twist` and `https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5829783/`.

4.4 DNA Nanostructures

Graphs made of DNA have been proposed in the last 20 years, but many associated mathematical questions remain unanswered. In particular questions remain open related to the graph meshes made of a DNA scaffold following DNA origami principles. We discussed many questions such as what types of graphs can be constructed with a knotted scaffold and what is the maximal complexity (in terms of knotting) a graph can achieve. Other questions related to the chirality of the DNA structures and units within crystals showed up, such as whether the chirality is intrinsic to the given unit and whether it can be explained mathematically.

5 Outcome of the Meeting

The short-term objectives of the proposed workshop were to:

1. Expand the mathematical toolbox to study the entanglement of nucleic acids by introducing combinatorialists to methods grounded in knot theory and, by introducing topologists to discrete models.

2. Update the mathematicians on current experimental procedures and designs to detect spatial arrangements of multi-stranded DNA/RNA complexes.

3. Develop new interdisciplinary approaches and collaborations to tackle emerging questions on the shape of multi-stranded DNA/RNA complexes.

4. Actively foster equity, diversity and inclusion in STEM fields by creating opportunities for early-career researchers to broaden their research networks.

We achieved these objectives as outlined below.

The impact of this workshop was multifold. During the workshop, we explored the interplay between knot theory, combinatorics, topological graph theory, biochemistry and structural biology with the goals of advancing our understanding of multi-stranded nucleic acids and creating opportunities for multidisciplinary collaboration and training. Throughout the workshop, this sparked new mathematical questions and theories of intrinsic theoretical interest. In addition, the workshop style promoted discussions among theoreticians and experimentalists that encouraged new experimental designs and tests for a better understanding of multi-strand interactions *in vitro* and *in vivo*.

More specifically, the workshop provided an excellent venue for the community to meet and learn about the latest results in topological and combinatorial models related to three dimensional nucleic acid structures. There were many new connections that were initiated. For example, the New York University lab that is working on structural DNA nanotechnology initiated connections with L. Zechiedrich's lab who studies the effects of enzyme action on DNA topology. The combinatorial methods of C. Heitsch have found new connections with A. Rechnitzer's computational methods for sampling combinatorial objects.

Due to the workshop, sharing of mathematical methods to address various topological questions is being initiated, as well as sharing of experimental and computational methods (such as GitHub links) were initiated.

We believe that there will be new collaborations sprouting out of the workshop. W. Moltmaker (U. of Amsterdam) and M. Saito (U. of South Florida) started working on a common project aimed at developing invariants for knotoids that directly relate to the DNA nanostructures presented by S. Vecchioni.

The poster session was a very lively event that provided many interactions among the participants. In particular, F. Martinez Figueroa and P. Pongtanapaisan visited C. Soteros after the workshop for a week. F. Martinez Figueroa and C. Soteros had never met before the workshop, nor had they collaborated. Posters were posted until the end of the workshop.

Wednesday evening, after the short excursions, the participants met at the lounge where R. Scharein introduced his software KnotPlot and helped everyone with installation and its initial use. This software was found to be very useful for everyone working on knots and interested in DNA topology.

As proposed, the organizers hosted a well attended evening session about "Keeping your research in STEM alive". There was a lively open discussion related to work-life integration at all career stages. Several questions were addressed, including how to keep a research program active when there may be time constraints due to other work-related or family obligations.

In conclusion, the workshop allowed for extensive interaction between all participants. This has opened the door to further communication among participants. In particular, the participants indicated that they are all looking forward to another instalment of the workshop.

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