10w5100: Mathematics and physics of polymer entanglement: Emerging concepts and biomedical applications
Jan 10 – Jan 15, 2010

MEALS

*Breakfast (Buffet): 7:00–9:30 am, Sally Borden Building, Monday–Friday
*Lunch (Buffet): 11:30 am–1:30 pm, Sally Borden Building, Monday–Friday
*Dinner (Buffet): 5:30–7:30 pm, Sally Borden Building, Sunday–Thursday
Coffee Breaks: As per daily schedule, 2nd floor lounge, Corbett Hall
***Please remember to scan your meal card at the host/hostess station in the dining room for each meal.**

MEETING ROOMS

All lectures will be held in Max Bell 159 (Max Bell Building accessible by walkway on 2nd floor of Corbett Hall). LCD projector, overhead projectors and blackboards are available for presentations. Please note that the meeting space designated for BIRS is the lower level of Max Bell, Rooms 155–159. Please respect that all other space has been contracted to other Banff Centre guests, including any Food and Beverage in those areas.

SCHEDULE

Sunday

16:00	Check-in begins (Front Desk - Professional Development Centre - open 24 hours)
17:30–19:30	Buffet Dinner, Sally Borden Building
20:00	Informal gathering in 2nd floor lounge, Corbett Hall (if desired) Beverages and small assortment of snacks available on a cash honour-system.

Monday

7:00–8:45	Breakfast
8:45–9:00	Introduction and Welcome to BIRS by BIRS Station Manager, Max Bell 159
9:00–9:30	Jonathan Fogg, Supercoiling in DNA minicircles: To get the big picture, think small
9:30–10:00	Sarah Harris, Computer Simulations of DNA Supercoiling at the Atomic Level
10:00–10:30	Coffee Break, 2nd floor lounge, Corbett Hall
10:30–11:00	Steve Levene, Loop-mediated regulation by lac repressor: does DNA supercoiling play a role?
11:00–11:30	David Levens, Genome-wide functional correlation between transcription, DNA conformation and topology
11:30–13:00	Lunch
13:00–14:00	Guided Tour of The Banff Centre; meet in the 2nd floor lounge, Corbett Hall
14:00–14:30	Group Photo; meet on the front steps of Corbett Hall
14:30–15:00	Javier Arsuaga, Modeling of Chromosome Intermingling by Partially Overlapping Uniform Random Polygons
15:00–15:30	Jason Cantarella, Intrinsic Symmetries of Knots and Links
15:30–16:00	Coffee Break, 2nd floor lounge, Corbett Hall
16:00–16:30	Tetsuo Deguchi, Effective scaling approximations for knotting probability, topological swelling and the distance distribution of random knots
16:30–17:00	Dorothy Buck, Topological Analysis of DNA Knotting and Unknotting
17:30–19:30	Dinner

Tuesday

7:00–9:00	Breakfast
9:00–9:30	Rob Scharein, Bounds for the minimum step number of knots in the simple cubic lattice
9:30–10:00	Stu Whittington, Pattern theorems: What we know and what we wish we knew
10:00–10:30	Coffee Break, 2nd floor lounge, Corbett Hall
10:30–11:00	Andrew Rechnitzer, Counting knotted polygons (nearly)
11:00–11:30	Buks Janse Van Rensburg, Statistics of Knotted Lattice Polygons
11:30–13:30	Lunch
13:30–14:00	Lynn Zechiedrich, Supercoiled minicircles as gene therapy vectors
14:00–14:30	Michael F. Schmid, How can DNA get in and out of a virus capsid?
14:30–15:00	Coffee Break, 2nd floor lounge, Corbett Hall
15:00–15:30	Wei Yang, Lessons learnt from a DNA helicase UvrD
15:30–16:00	Wilma Olson, Protein-mediated DNA Looping and Gene Expression
17:30–19:30	Dinner

Wednesday

7:00–9:00	Breakfast
9:00–9:30	Bertrand Duplantier, Partition Function of a Freely-Jointed Chain in Half-Space
9:30–10:00	Michael Szafron, Knotting Probabilities Resulting from a Local Strand Passage in a Knot-type K SAP
10:00–10:30	Coffee Break, 2nd floor lounge, Corbett Hall
10:30–11:00	Teresita Ramirez-Rosas, Looking for a Lower Bound for the Number of Quadrisecants
11:00–11:30	Mahshid Atapour, Exponential Growth of the Number of n-edge Linked Clusters in Z^3 and the Consequences in Entanglement Percolation
11:30–13:30	Lunch
13:30–17:30	Free Afternoon
17:30–19:30	Dinner

Thursday

7:00–9:00	Breakfast
9:00–9:30	Phoebe Rice, Structural model for how Sin recombinase exploits topology
9:30–10:00	Georgi Muskhelishivili, General organisational principles of the transcriptional regulation system: a tree or a circle?
10:00–10:30	Coffee Break, 2nd floor lounge, Corbett Hall
10:30–11:00	Jue D. Wang, Co-orientation of Replication and Transcription Preserves Genome Integrity
11:00–11:30	Tim Hughes, High nucleosome occupancy is encoded at human regulatory sequences
11:30–13:30	Lunch
13:30–14:00	Hue Sun Chan, Selective Segment Passages at Hooked and Twisted Juxtapositions Consistently Rationalize the Decatenating, Unknotting and Supercoil-Tightening Actions of Type-2 Topoisomerases
14:00–14:30	Cristian Micheletti, Coarse-grained simulations of DNA in confined geometries
14:30–15:00	Coffee Break, 2nd floor lounge, Corbett Hall
15:00–15:30	Yitzhak Rabin, Coupling of Twist and Writhe in Short DNA Rings
15:30–16:00	Alexander Grosberg, Large scale organization of DNA in chromosomes
17:30–19:30	Dinner

Friday

7:00–9:00	Breakfast
9:00–	Informal Discussions
10:00–10:30	Coffee Break, 2nd floor lounge, Corbett Hall
11:30–13:30	Lunch

Checkout by 12 noon.

** 5-day workshops are welcome to use the BIRS facilities (2nd Floor Lounge, Max Bell Meeting Rooms, Reading Room) until 3 pm on Friday, although participants are still required to checkout of the guest rooms by 12 noon. **

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ABSTRACTS

Speaker: **Javier Arsuaga** (San Francisco State University)
Title: *Modeling of Chromosome Intermingling by Partially Overlapping Uniform Random Polygons*
Abstract: During the early phase of the cell cycle the eukaryotic genome is organized into chromosome territories. The geometry of the interface between any two chromosomes remains a matter of debate and may have important functional consequences. The Interchromosomal Network model (introduced by Branco and Pombo) proposes that territories intermingle along their periphery. In order to partially quantify this concept we here investigate the probability that two chromosomes form an unsplittable link. We use the uniform random polygon as a crude model for chromosome territories and we model the interchromosomal network as the common spatial region of two overlapping uniform random polygons.

This simple model allows us to derive some rigorous mathematical results as well as to perform computer simulations easily. We find that the probability that one uniform random polygon of length n that partially overlaps a fixed polygon is bounded below by $1 - O(1/sqrt(n))$. We use numerical simulations to estimate the dependence of the linking probability of two uniform random polygons on the amount of overlapping. We propose that this dependence relation may be modeled as $1 - \frac{ae+b(1-e)}{e\sqrt{mn}+b(1-e)}$ where $e > 0$. We then use these results to model the data published by Branco and Pombo and observe that for the amount of overlapping observed experimentally the URPs have a non-zero probability of forming an unsplittable link.

This is joint work with Y. Diao and R. Scharein.

Speaker: **Mahshid Atapour** (York University)
Title: *Exponential Growth of the Number of n-edge Linked Clusters in Z^3 and the Consequences in Entanglement Percolation*
Abstract: An animal in the simple cubic lattice is a finite connected subgraph of Z^3. Let a_n be the number (up to translation) of n-edge animals in Z^3. In 1967, Klarner proved that a_n grows exponentially. Let e_n be the number (up to translation) of all n-edge linked clusters, i.e. subgraphs of Z^3 in which the connected components (animals) are (topologically) non-splittable. In this talk, I briefly explain how it can be proved that e_n also has a finite exponential growth rate. I also mention some of the important consequences of this result in entanglement percolation.

Speaker: **Dorothy Buck** (Imperial College)
Title: *Topological Analysis of DNA Knotting and Unknotting*
Abstract: This is joint work with Ken Baker and Andrew Lobb.

Many protein-DNA interactions, such as site-specific recombination and (type II) topoisomerase-mediated unknotting and unlinking, act by cutting and resealing (double-stranded) DNA segments in a localized way. These enzymatic reactions can be modelled in terms of tangles, 3-dimensional balls with two properly embedded arcs, each representing a segment of DNA. The action of the protein can be thought of as removing one tangle and replacing it with another – e.g. a topoisomerase-initiated crossing change as replacing a (+1) tangle with a (-1) tangle – leaving the rest of the DNA unchanged. This replacement can be straightforward (as in the topoisomerase example above) or quite complex.

Because of the plectonemic supercoiling of DNA, 'rational tangles' (formed by an alternating series of horizontal and vertical twists) are the most biologically relevant. We classify all possible rational tangles that can replace – in any prescribed manner – a given rational tangle, thus elucidating all possible protein-mediated localized changes of DNA.

Speaker: **Jason Cantarella** (University of Georgia)
Title: *Intrinsic Symmetries of Knots and Links*
Abstract: Given a link composed of several circular strands of DNA, each component is oriented and uniquely labeled by its sequence of base pairs. Can these components be reoriented? Can they switch places? The group of transformations of this type which can be realized by an isotopy of the link is called the "intrinsic" symmetry group of the link. We present the first computations of the intrinsic symmetry groups of links with 8 and fewer crossings.

The traditional definition of the symmetry group of a link is the mapping class group $MCG(S^3, L)$ of the pair S^3, L. Our symmetry groups are the images of the traditional symmetry groups of links under the natural homomorphism from $MCG(S^3, L)$ onto $MCG(S^3) \times MCG(L)$.

Speaker: **Hue Sun Chan** (University of Toronto)
Title: *Selective Segment Passages at Hooked and Twisted Juxtapositions Consistently Rationalize the Decatenating, Unknotting and Supercoil-Tightening Actions of Type-2 Topoisomerases*
Abstract: The mathematical basis of the hypothesis that type-2 topoisomerases recognize and act at specific DNA juxtapositions has been investigated by coarse-grained lattice polymer models, showing that selective segment passages at "hooked" juxtapositions can result in dramatic reductions in catenane and knot populations. The lattice modeling approach is now extended to account for the hallmark narrowing of variance of linking number (Lk) of DNA circles by type-2 topoisomerases. In general, the steady-state variance of Lk resulting from selective segment passages at a specific juxtaposition geometry j is inversely proportional to the average linking number, $\langle Lk \rangle_j$, of circles with the given juxtaposition. Based on this formulation, we demonstrate that selective segment passages at "hooked" and "twisted" juxtapositions reduce the variance of Lk. The dependence of this effect on model DNA circle size is remarkably similar to that observed experimentally for type-2 topoisomerases, which appear to be less capable in narrowing Lk variance for small DNA circles than for larger DNA circles. This behavior is rationalized by a substantial cancellation of writhe in small circles with hook-like juxtapositions. For an extended set of juxtapositions in our model, we detect a significant correlation between the juxtapositions' supercoil simplification potential and their logarithmic decatenating potential as well as their logarithmic unknotting potential, a trend reminiscent of scaling relations between corresponding experimental measurements on type-2 topoisomerases from a variety of organisms. The consistent agreements between theory and experiment we have achieved argue strongly for type-2 topoisomerase action at hook- or twist-like DNA juxtapositions.

Speaker: **Tetsuo Deguchi** (Ochanomizu University)
Title: *Effective scaling approximations for knotting probability, topological swelling and the distance distribution of random knots*
Abstract: We discuss various scaling approximations for the probability of random knotting and the mean square radius of gyration for random knots as functions of the number of segments. We also introduce an effective scaling formula for the distribution of distance between two segments of polygon.

For an illustration, let us consider knotting probability. For off-lattice models we numerically evaluate the probability of random knotting as a function of the number of nodes. We then find that two types of fitting formulas are quite effective, one for describing asymptotic behavior and another one for describing finite-size random knotting probability. Although the latter formula should be vailid for a limited range of the number of nodes, it has nice facotrization property by which we can predict the probability of composite knots from those of the constituent prime knots.

The scaling approximations particularly effective for finite-size random knots should be fundamental in application to real ring polymers, since all ring polymers have some finite number of segments. The results of the present talk can be checked in experiments near future.

Speaker: **Bertrand Duplantier** (Centre Energie Automique / Saclay)
Title: *Partition Function of a Freely-Jointed Chain in Half-Space*
Abstract: When lecturing about the Physics of Biological Polymers in 2007 at EPFL (Lausanne), I was

asked by A. Stasiak about the statistics of a discrete freely-jointed chain anchored at a plane in three space, and under traction by a force. This problem is relevant to the description of DNA under traction and of proteins in translocation across a membrane. Surprisingly, the calculation of the canonical partition function appears as non-trivial, and must be done via a functional recursion over the number of monomers. The enumeration of configurations also involves specific combinatorial aspects, which bring in cell decompositions, Motzkin paths and bijections to trees, a long way from the original biological question!

This is joint work with Olivier Bernardi and Philippe Nadeau.

Speaker: **Jonathan Fogg** (Baylor College of Medicine)
Title: *Supercoiling in DNA minicircles: To get the big picture, think small*
Abstract: DNA supercoiling has a dramatic effect on its function. Indeed, for many biological processes a distinct threshold of supercoiling must be reached before the reaction can occur. Although the global conformational changes that occur as a result of supercoiling are reasonably well understood, relatively little is known about the consequences of DNA supercoiling on the local level. These sequence-specific conformational changes must surely dictate how proteins recognize and metabolize DNA. Even the largest DNA binding proteins are very small relative to chromosomal or plasmid DNA and are, therefore, unable to sense global DNA topology.

We have developed and utilized a protocol to produce milligram quantities of supercoiled minicircle DNA, as small as 250 bp (Fogg et al. 2006). Individual topoisomers were isolated ranging from $\sigma = +0.08$ to -0.19. Our supercoiled minicircle substrates provide a unique insight into the local DNA structure of supercoiled DNA and how this is recognized and manipulated by enzymes. Several unexpected aspects of supercoiled DNA were revealed from our studies of DNA minicircles. We discovered that the addition or subtraction of three base pairs has a profound effect on the gel electrophoretic mobility of small DNA circles. The topoisomers of a 336 bp minicircle display a very regular pattern of electrophoretic mobility. When we generated topoisomers of 333 bp and 339 bp minicircles, however, several of these minicircles show unexpected electrophoretic behavior. We also discovered a topoisomer that appears to flip between open and writhed conformations, akin to the "frustrated" minicircles detected in computational simulations (Harris et al. 2008). Notably, we found that positively supercoiled minicircles have a much higher propensity to writhe than negatively supercoiled minicircles, even in the absence of added divalent metal ions. In contrast, limited writhe was observed for negatively supercoiled minicircles in the absence of added divalent metal ions, demonstrating the importance of electrostatic effects on DNA structure. Many models of DNA elasticity incorrectly assume that positively supercoiled DNA is equal and opposite to negatively supercoiled DNA. Our findings prove there is a distinct asymmetry.
References cited:
Fogg et al. (2006) Journal of Physics Condensed Matter. 18, S145-S159
Harris et al. (2008) Nucleic Acids Research 36, 21-29

Speaker: **Alexander Grosberg** (New York University)
Title: *Large scale organization of DNA in chromosomes*
Abstract: Recent experiments confirmed an old theoretical prediction that human genome (and presumably that of other eukaryotes) on the large scale (above the nucleosome size) is organized in the form of crumpled fractal globule stabilized by the topological effects.

Speaker: **Sarah Harris** (University of Leeds)
Title: *Computer Simulations of DNA Supercoiling at the Atomic Level*
Abstract: The discovery of the structure of duplex DNA revealed how cells store genetic information. However, we are far from understanding the more complex biological question of how this information is regulated and processed by the cell. DNA topology and supercoiling is known to affect DNA transcription as changes in topology affect DNA conformation, and can thereby modify the interaction between regulatory DNA-binding proteins and their target sites.

Small DNA circles offer a controllable model system for the systematic exploration of the dependence of DNA structure on supercoiling. We use computer simulation to explore the supercoiling-dependent conformation of small DNA circles, in particular their writhe, and how this is affected by supercoiling, salt concentration, DNA sequence and the size of the circles [1]. The calculations use atomistic molecular dynamics simulation, and employ both implicit and explicit solvent models. We have been systematically testing our computational models against experimental data [2] for small circles of between 65 and 214 base pairs. We have also been investigating the supercoiling-dependent binding of a 3rd DNA strand (triplex formation) to a target site within a writhed DNA circle for comparison with experimental data [3]. These preliminary calculations are designed to explore the thermodynamics of supercoiling-dependent binding, and use triplex formation as a model system for exploring the importance of supercoiling in DNA recognition in general.

[1] Harris, S. A., Laughton, C. A. & Liverpool, T. B. (2008). Mapping the phase diagram of the writhe of DNA nanocircles using atomistic molecular dynamics simulations. Nucleic Acids Res 36, 21-9.
[2] Du, Q., Kotlyar, A. & Vologodskii, A. (2008). Kinking the double helix by bending deformation. Nucleic Acids Res. 36, 1120-1128.
[3] Maxwell, A., Burton, N. P. & O'Hagan, N. (2006). High-throughput assays for DNA gyrase and other topoisomerases. Nucleic Acids Res 34, e104.

Speaker: **Tim Hughes** (University of Toronto)
Title: *High nucleosome occupancy is encoded at human regulatory sequences*
Abstract: Active eukaryotic regulatory sites are characterized by open chromatin, and yeast promoters and transcription factor binding sites (TFBSs) typically have low intrinsic nucleosome occupancy - i.e. these sequences are disfavored when naked DNA and histone octamers are assembled in vitro. Here, we show that in contrast to yeast, DNA at human promoters, enhancers, and TFBSs generally encodes high intrinsic nucleosome occupancy. In most cases we examined, these elements also have high experimentally measured nucleosome occupancy in vivo. These regions typically have high G+C content, which correlates positively with intrinsic nucleosome occupancy, presumably due to high bend, twist, tip etc. parameters, as well as reduced probability of rigid, nucleosome-excluding polyA-like sequences. We propose that high nucleosome affinity is directly encoded at regulatory sequences in the human genome to restrict access to regulatory information that will ultimately be utilized in only a subset of differentiated cells. We also propose that nucleosomes may play direct roles in the function of active enhancers. Our findings also present a functional consequence of variation in base content that is observed at diverse scales in eukaryotic genomes.

Speaker: **Buks Janse Van Rensburg** (York University)
Title: *Statistics of knotted lattice polygons*
Abstract: Polygons in the cubic lattice are simple closed curves in three space and have well-defined knot types. The number of lattice polygons of length n and knot type K in the cubic lattice is $p_n(K)$, where we consider two polygons to be equivalent under translations in the lattice. For example, if K is the unknot $\emptyset$, then $p_4(\emptyset) = 3$, $p_6(\emptyset) = 22$, $p8(\emptyset) = 207$ and so on. Determining $p_n(K)$ for arbitrary n and knot types K is a difficult numerical problem, but the GAS-algorithm can be used for approximate enumeration of $p_n(K)$. In this talk I shall present the results of simulations to estimate the approximate values of $p_n(K)$ for some knot types K. The scaling of $p_n(K)$ will be discussed, and evidence will be presented that $p_n(K) \sim A_K n^{\alpha-2+N_K} \mu_\emptyset^n$; where N_K is the number of prime components in the knot type K and $\mu_\emptyset$ is the growth constant for unknotted polygons. The relative frequencies of knot types in lattice polygons will also be discussed.

This is joint work with Andrew Rechnitzer.

Speaker: **Steve Levene** (University of Texas at Dallas)
Title: *Loop-mediated regulation by lac repressor: does DNA supercoiling play a role?*
Abstract: Interactions of *E. coli lac* repressor (LacI) with a pair of operator sites on the same DNA molecule can lead to the formation of looped nucleoprotein complexes both *in vitro* and *in vivo*. The *lac* system is

a major paradigm for loop-mediated gene regulation in prokaryotic cells; however, the complex interplay between DNA topology, modulation of chromosome topology by architectural-DNA binding proteins, and loop-mediated regulation remain poorly understood. We discuss effects of DNA supercoiling on LacI-mediated looping *in vitro* investigated by a combination of fluorescence resonance energy transfer studies, semi-analytical DNA elasticity calculations, and Monte Carlo simulation.

Speaker: **David Levens** (Center for Cancer Research NIH)
Title: *Genome-wide functional correlation between transcription, DNA conformation and topology*
Abstract: We are investigating the role of dynamic supercoiling in the regulation of gene expression and DNA structure in vivo and in vitro. We have developed a method to map unpaired bases across the genome using potassium permanganate. Besides the expected signature of transcription bubbles at promoters, other sites of non-B-DNA occurring outside of genes were often sensitive to transcription inhibition, suggesting a long-distance coupling between transcription and DNA conformation via transmission of mechanical stress (dynamic supercoils). Such stress is generated as DNA is threaded through the RNA polymerase active site and propagated to remote sequences. Supercoil sensitive unusual DNA structures may contribute to the real-time self-regulation of many genes. Previously we have demonstrated the existence and measured the magnitude of such dynamical supercoils in vivo. Now, we have developed an approach to build a genome-scale map of DNA supercoiling using psoralen intercalation as a probe. The map shows that negative supercoiling often propagates to or beyond 2 kb upstream of active promoters. This supercoiling contributes to the formation of a variety of non-B DNAs, including quadruplex and Z-DNA. These non-B DNA structures may be recognized by proteins and contribute to a variety control mechanisms. Overlaying the maps of DNA supercoiling and conformation with the in vivo binding sites of structure-sensitive transcription factors as well as sites of topoisomerase I and II action may reveal new modes of transcriptional regulation on a global scale.

Speaker: **Cristian Micheletti** (International School for Advanced Studies)
Title: *Coarse-grained simulations of DNA in confined geometries*
Abstract: The packing of DNA inside bacteriophages arguably yields the simplest example of genome organisation in living organisms. An indirect indication of how DNA is packaged is provided by the detected spectrum of knots formed by DNA that is circularised inside the P4 viral capsid. The experimental results on the knot spectrum of the P4 DNA are compared to results of coarse-grained simulation of DNA knotting in confined volumes. We start by considering a standard coarse-grained model for DNA which is known to be capable of reproducing the salient physical aspects of free (unconstrained) DNA. Specifically the model accounts for DNA bending rigidity and excluded volume interactions. By subjecting the model DNA molecules to spatial confinement it is found that confinement favours chiral knots over achiral ones, as found in the P4 experiments. However, no significant bias of torus over twist knots is found, contrary to what found in P4 experiments. A good consistency with experiment is found, instead, upon introducing an additional interaction potential accounting for tendency of contacting DNA strands to order as in cholesteric liquid crystals. The degree of localization of the obtained knots is finally discussed in connection with the process of genome ejection out of the phage.

Speaker: **Georgi Muskhelishivili** (Jacobs University)
Title: *General organisational principles of the transcriptional regulation system: a tree or a circle?*
Abstract: The fundamental problem in attempting a holistic description of transcriptional regulation system is of methodological nature and lies in the necessity of integrating the systemic and structural-molecular views. Recent advances of systemic approaches to gene expression provide unforeseen opportunities for relating extensive datasets describing the transcriptional regulation system as a whole. However, due to the multifaceted nature of the phenomenon, these datasets often contain logically distinct types of information determined by underlying approach and adopted methodology of data analysis. Consequently, to integrate the datasets comprising information on the states of chromatin structure, transcriptional regulatory network and cellular metabolism, a novel methodology enabling interconversion of logically distinct

types of information is required. Here we provide a holistic conceptual framework for analysis of global transcriptional regulation as a system coordinated by structural coupling between the transcription machinery and DNA topology, acting as interdependent sensors and determinants of metabolic functions. In this operationally closed system any transition in physiological state represents an emergent property determined by shifts in structural coupling, whereas genetic regulation acts as a genuine device converting one logical type of information into the other.

Speaker: **Wilma Olson** (Rutgers University)
Title: *Protein-mediated DNA looping and gene expression*
Abstract: Making sense of gene regulation in living systems requires understanding of the looping properties of DNA in crowded, multi-component systems. The presence of non-specific binding proteins that introduce sharp bends, localized untwisting, and/or dislocation of the DNA double-helical axis, stabilizes functional repression loops ranging from as few as 65 base pairs to as many as tens of thousands of base pairs. As a first step in the analysis of such looping, we have investigated the effects of various proteins on the configurational properties of fragments of DNA, treating the DNA at the level of base-pair steps and incorporating the known effects of various proteins on DNA double-helical structure. The presentation will highlight some of the new models and computational techniques that we have developed to generate the three-dimensional configurations of protein-mediated DNA loops and illustrate new insights gained from this work about the effects of various proteins on DNA topology and the apparent contributions of the non-specific binding proteins to gene expression.

Speaker: **Yitzhak Rabin** (Bar-Ilan University)
Title: *Coupling of Twist and Writhe in Short DNA Rings*
Abstract: While bending and twist can be treated as independent degrees of freedom for linear DNA molecules, the loop closure constraint introduces a coupling between these variables in circular DNA. We performed Monte Carlo simulations of worm-like rods with both bending and twist rigidity, in order to study the coupling between the writhe and twist distributions for various DNA lengths. We find that for sufficiently short DNA, the writhe distribution differs significantly from that of a model with bending energy only. We show that the factorization approximation introduced by previous researchers coincides, within numerical accuracy, with our simulation results, and conclude that the closure constraint is fully accounted for by the White-Fuller relation.

Speaker: **Teresita Ramirez-Rosas** (Grand Valley State University)
Title: *Looking for a lower bound for the number of quadrisecants*
Abstract: We have been interested in finding a lower bound for the number of quadrisecants for a polygonal knot in general position in terms of its crossing number. Our immediate goal is to show the following:
Conjecture: A knot K with crossing number, $cr(K)$, has at least $\frac{1}{2}\left(\frac{2cr(K)+1}{3}\right)^2$ quadrisecants.

In this talk I will discuss some ideas that might lead us to find a lower bound for the number of quadrisecants. In particular, I will talk about one of the results we have that can help us to solve this conjecture: given $x \in K$ the number of trisecants with starting or ending point at x is at least $\frac{2cr(K)+1}{3}$.

Speaker: **Andrew Rechnitzer** (University of British Columbia)
Title: *Counting knotted polygons (nearly)*
Abstract: The Rosenbluth method of simulating self-avoiding walks has become one of the standard methods for studying polymer statistics. The algorithm was originally developed in the 1950s by Hammersley & Morton and Rosenbluth & Rosenbluth, but suffered from poor convergence. This changed in the mid 90s with Grassberger's development of a pruned and enriched implementation called PERM. It was soon followed by multicanonical and flat-histogram implementations which have become indispensable tools for exploring the critical behaviour of polymer systems.

Combinatorially, one can think of the Rosenbluth method as a technique of "approximate enumeration" which produces precise estimates of the number of conformations of a particular size and energy. This

same method can then be applied to many other combinatorial problems provided there is a unique and unambiguous way of constructing the underlying objects. Unfortunately, self-avoiding polygons (SAPs) are not such a system.

In this talk I will discuss this history and describe two recent extensions of the original Rosenbluth algorithm which allow the approximate enumeration of two-dimensional SAPs and SAPs of fixed knot type in three dimensions.

This is joint work with Buks van Rensburg.

Speaker: **Phoebe Rice** (University of Chicago)
Title: *Structural model for how Sin recombinase exploits topology*
Abstract: Sin is a DNA recombinase belonging to the serine resolvase family. For various biological reasons, these enzymes convert 1 large DNA circle into 2 smaller ones. To prevent other recombination products, the system is regulated by a "topological filter" - it is only enzymatically active when the two partner sites are brought together in a synaptic complex containing 3 interdomainal supercoiling nodes.

Using crystal structures of individual components, we have constructed a 3-dimensional model for this synaptic complex. We are also using biochemical assays to address the details of how this catalytic regulation is enforced. Finally, we have preliminary data showing that a different serine resolvase, Tn3, uses different protein-DNA interactions to construct a regulatory complex with the same DNA topology.

Speaker: **Rob Scharein** (Hypnagogic Software)
Title: *Bounds for the minimum step number of knots in the simple cubic lattice*
Abstract: Knots are found in DNA as well as in proteins, and they have been shown to be good tools for structural analysis of these molecules. An important parameter to consider in the artificial construction of these molecules is the minimum number of monomers needed to make a knot. Here we address this problem by characterizing, both analytically and numerically, the minimum length (also called minimum step number) needed to form a particular knot in the simple cubic lattice. Our analytical work is based on improvement of a method introduced by Diao to enumerate conformations of a given knot type for a fixed length. This method allows us to extend the previously known result on the minimum step number of the trefoil knot 3_1 (which is 24) to the knots 4_1 and 5_1 and show that the minimum step numbers for the 4_1 and 5_1 knots are 30 and 34, respectively. Using an independent method based on the BFACF algorithm, we provide a complete list of numerical estimates (upper bounds) of the minimum step numbers for prime knots up to ten crossings, which are improvements over current published numerical results. We enumerate all minimum lattice knots of a given type and partition them into classes defined by BFACF type-0 moves.

This work is in collaboration with K. Ishihara, J. Arsuaga, Y. Diao, K. Shimokawa and M. Vazquez.

Speaker: **Michael F. Schmid** (Baylor College of Medicine)
Title: *How can DNA get in and out of a virus capsid?*
Abstract: Double stranded DNA phages and viruses encapsidate their genome into a preformed capsid shell through one icosahedral vertex, which contains a portal protein complex. ATP is consumed, and the DNA is inserted, probably involving twisting. Extrusion of the DNA during cell or bacterial infection is accomplished through the same vertex.

Our lab (National Center for Macromolecular Imaging, BCM) has determined the structure of several phages and viruses by cryoelectron microscopy (cryoEM). This technique aligns and averages thousands of individual 2D projection images in random orientations to produce a 3D reconstruction of the virus. Recently we have been able to perform this reconstruction without applying icosahedral symmetry, thus we are able to see the unique vertex and the other non-icosahedral features. Clues as to the packing of the DNA include: 1) concentric shells of DNA spooled around the axis defined by the unique vertex, 2) a roughly hexagonal packing of the DNA helices against each other, 3) the terminus (last in) of the DNA runs up the axis toward the portal, among others. Many questions remain.

Speaker: **Michael Szafron** (University of Saskatchewan)
Title: *Knotting Probabilities Resulting from a Local Strand Passage in a Knot-type K SAP*

Abstract: DNA is prone to several topological entanglement problems. One such problem is that knotted DNA cannot be successfully replicated. This problem is resolved via an interaction between topoisomerase enzymes and the DNA. These enzymes interact locally with DNA and allow one strand of DNA to pass through itself. Because these local strand passages can potentially change the knot-type of DNA, the frequency of the knots produced can be used to characterize topoisomerase action on DNA topology.

As a first step towards understanding this action, a self-avoiding polygon (SAP) model has been designed to investigate the effect of random local strand passages on the knot-type of a ring polymer. For increasing SAP sizes, the limiting knot transition probability estimates obtained from Monte Carlo data for this model will be presented. Evidence will be provided that these limiting knot transition probabilities depend on the local juxtaposition at the strand passage site.

Speaker: **Jue D. Wang** (Baylor College of Medicine)
Title: *Co-orientation of Replication and Transcription Preserves Genome Integrity*
Abstract: In many bacteria, there is a genome-wide bias towards co-orientation of replication and transcription, with essential and/or highly expressed genes further enriched co-directionally. We previously found that reversing this bias in the bacterium Bacillus subtilis slows replication elongation, and proposed that this effect contributes to the evolutionary pressure selecting the transcription-replication co-orientation bias. This selection might have been based purely on selection for speedy replication; alternatively, the slowed replication might actually represent an average of individual replication-disruption events, each of which is counter-selected independently because genome integrity is selected. To differentiate these possibilities and define the precise forces driving this aspect of genome organization, we generated new strains with inversions either over 1/4 of the chromosome or at ribosomal RNA (rRNA) operons. Applying mathematical analysis to genomic microarray snapshots, we found that replication rates vary dramatically within the inverted genome. Replication is moderately impeded throughout the inverted region, which results in small but significant competitive disadvantage in minimal medium. Importantly, replication is strongly obstructed at inverted rRNA loci in rich medium. This obstruction results in disruption of DNA replication, activation of DNA damage response, loss of genomic integrity and cell death. Our results strongly suggest that preservation of genome integrity drives the evolution of co-orientation of replication and transcription, a conserved feature of genome organization.

Speaker: **Stu Whittington** (University of Toronto)
Title: *Pattern theorems: What we know and what we wish we knew*
Abstract: Pattern theorems are a way to show that certain events occur with high probability, and were used to show that lattice polygons (a model of ring polymers) are knotted with high probability when the polygon is large. Over the last twenty years new ways to prove pattern theorems have emerged and pattern theorems have been proved for new situations. This talk will review the idea behind pattern theorems and will show how they can be used to prove results about topological and geometrical entanglement complexity. In spite of the progress made recently there are still many areas where a pattern theorem would be useful or where a sharper form of a pattern theorem would give improved results. Some of these open questions will be discussed.

Speaker: **Wei Yang** (NIH)
Title: *Lessons learnt from a DNA helicase UvrD*
Abstract: How do molecular motors convert chemical energy to mechanical work? Helicases and nucleic acids offer simple motor systems for extensive biochemical and biophysical analyses. Atomic resolution structures of UvrD-like helicases complexed with DNA in the presence of AMPPNP, ADPPi, and Pi reveal several salient points that aid understanding mechano-chemical coupling. Each ATPase cycle causes two motor-domains to rotationally close and open. At a minimum, two motor-track contact points of alternating tight and loose attachment convert domain rotations to uni-directional movement. A motor is poised for action only when fully in contact with its track and, if applicable, working against a load. The orientation of domain rotation relative to the track determines whether the movement is linear, spiral or

circular. Motors powered by ATPases likely deliver each power stroke in two parts, before and after ATP hydrolysis.

Speaker: **Lynn Zechiedrich** (Baylor College of Medicine)
Title: *Supercoiled minicircles as gene therapy vectors*
Abstract: To study DNA supercoiling and DNA topoisomerases, we created a way to make milligram quantities of minicircle DNAs of a few hundred base pairs. These DNAs have been extremely useful for this purpose and Jonathan Fogg will be discussing this work. I will present data showing that supercoiled minicircles are superior vectors for delivering DNA into human cell types that no other DNA vector has been previously able to penetrate. In cells, DNA sequence is transcribed from these minicircles into small RNAs that regulate gene expression. Even small genes can be expressed from supercoiled minicircles. Supercoiled minicircles resist sheer forces associated with gene therapy delivery and are significantly less susceptible to the nucleases in human serum than normal plasmid DNA vectors of a few thousand base pairs. These data show that supercoiled minicircles are a promising new tool for gene delivery.