Banff International Research Station
for Mathematical Innovation and Discovery

Banff workshop - Entanglement in biology; how Nature controls the topology of proteins and DNA November 17 – 22, 2013

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, in the foyer of the TransCanada Pipeline Pavilion (TCPL)
***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 the lecture theater in the TransCanada Pipelines Pavilion (TCPL). An LCD projector, a laptop, a document camera, and blackboards are available for presentations.

SCHEDULE

Sunday

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

Monday

7:00-8:45	Breakfast
8:45-9:00	Introduction and Welcome by BIRS Station Manager, TCPL
9:00-9:30	W. Minor
9:30-10:00	S. Plotkin
10-10:30	S. Jackson
10:30-11:00	Coffee Break, TCPL
11:00-11:30	J. Onuchic
11:30-12:00	E. Haglund
12:00-13:00	Lunch

14:00-14:30	J. Cantarella
14:30-15:00	C. Ernst
15:00-15:30	Coffee Break, TCPL
15:30-16:00	K. Shimokawa
16:30-16:30	E. Panagiotou
16:30-17:00	S. Whittington
17:30-19:30	Dinner

Tuesday

7:00-9:00	Breakfast
9:00-9:30	M. Cieplak
9:30-10:00	P. Szymczak
10:00-10:30	H. Li
10:30-11:00	Coffee Break, TCPL
11:00-11:30	Group Photo; meet in foyer of TCPL (photograph will be taken outdoors so a jacket might be required)
11:30-12:00	P. Virnau
12:00-14:00	Lunch
14:00-14:30	J. Arsuaga
14:30-15:00	T. Deguchi
15:00-15:30	Coffee Break, TCPL
15:30-16:00	van Rensburg
16:00-16:30	J. Kadomatsu
16:30-17:00	G. Dietler
17:30-19:30	Dinner

Wednesday

7:00-9:00	Breakfast
9:00-9:30	M. Nicodemi
9:30-10:00	A. Stasiak
10:00-10:30	A. Grosberg
10:30-11:00	Coffee Break, TCPL
11:00-11:30	Free Time
11:30-13:30	Lunch
	Free Afternoon
17:30-19:30	Dinner

Thursday

7:00-9:00	Breakfast
9:00-9:30	J. Schvartzman
9:30-10:00	D. Buck
10:00-10:30	M. Vazquez
10:30-11:00	Coffee Break, TCPL
11:00-11:30	D. Catanase
11:30-12:00	S.Harris
12:00-14:00	Lunch

14:00-14:30 K. Millett
14:30-15:00 C. Soteros
15:00-15.30 Coffee Break, TCPL
15:30-16:00 M. Szafron
16:00-16:30 C. Micheletti
16:30-17:00 D. Sumners
17:30-19:30 Dinner

Friday

7:00-9:00 Breakfast
9.30-10:30 General discussion
10:30-11:30 I. Darcy
11:30-12:00 Concluding remarks
11:30-13:30 Lunch

Checkout by 12 noon.

** 5-day workshop participants are welcome to use BIRS facilities (BIRS Coffee Lounge, TCPL and 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

(in alphabetic order by speaker surname)

Speaker: **Arsuaga, Javier** (San Francisco State University, USA)
Title: *Modelling the kinetoplast DNA network*
Abstract: Kinetoplast DNA (kDNA) is an extraordinarily complex DNA structure found in the mitochondrion of Trypanosomatida. Kinetoplast DNA contains thousands of small circular DNA molecules that are topologically linked into a network. Experimental results in Crithidia fasciculata have shown that every minicircle in the network is singly linked to an average of three other minicircles (i.e. it has valence 3). This low valence value is in sharp contrast with results obtained by computer simulations that predict a much higher valence value. To address this problem we quantify the effect that different network parameters have in the relationship between minicircle density and valence; this include the relative position of minicircles, minicircle flexibility, minicircle volume exclusion and minicircle relative orientation. We conclude that the relative orientation of minicircles is the main factor that increases the high density of minicircles while keeping the valence value small.
Work in collaboration with Y. Diao, K. Hinson, M. Klingbeil and V. Rodriguez.

Speaker: **Buck, Dorothy** (Imperial College, England)
Title: *Knotted DNA: Mathematical Models and Biological Consequences*
Abstract: We'll discuss recent work on knotted and linked DNA molecules. Using several case studies as examples, we'll consider the topological techniques used to model the processes that knot and link DNA. We'll explore the biological ramifications of DNA knotting and linking, and how the results of these topological models can inform experimentalists.

Speaker: **Cantarella, Jason** (University of Georgia, USA)
Title: *New algorithms for sampling closed and/or confined equilateral polygons*
Abstract: This talk gives an overview of new Markov chain methods based on symplectic geometry for understanding and sampling spaces of fixed edgelength polygons. The new methods are simple to code, and allow you to sample polygons in several different confinement models, as well as to prove some theorems about closed and confined random polygons. These are the first Markov chain methods for closed and confined

polygons with a proof of geometric convergence to the correct probability measure on polygon space and statistically consistent error estimators for Markov chain Monte Carlo integration.
The talk describes joint work with Clayton Shonkwiler (UGA).

Speaker: **Catanese, Jr, Daniel J.** (Baylor College of Medicine, Houston, USA)
Title: *Multidisciplinary approaches converge to reveal the active structures of DNA*
Abstract: The double-helical structure of DNA imparts incredible stability, protecting the encoded genetic information from chemical and mechanical stress. Hydrophobic bases, the molecular readout of the genetic code, are buried within the interior of the helix. In contrast, the monotonous, hydrophilic, highly negatively charged sugar-phosphate backbone that contains no genetic information forms the accessible DNA exterior. The same stability that makes relaxed B-form DNA the safe repository of the genetic code prevents access to the information encoded by the bases. We hypothesized that the seemingly contradictory requirements of genetic stability and DNA activity are accomplished via a tightly-regulated switch whereby torsional strain causes localized structural alterations, including base-flipping, denaturation and other non-canonical, non-B DNA structures. We used a multidisciplinary collaborative approach to demonstrate that our hypothesis was correct. The structural alterations brought about by torsional stress, likely base-flipping and denaturation in the underwound, negatively supercoiled direction and P-like DNA in overwound, positively supercoiled direction, facilitate access to the genetic code to initiate DNA activity and recruit DNA-acting enzymes.
Work in collaboration with Daniel J. Catanese, Jr., Jonathan M. Fogg, Rossitza N. Irobalieva, Michael F. Schmid, Wah Chiu, and Lynn Zechiedrich

Speaker: **Cieplak, Marek** (Polish Academy of Sciences, Warsaw, Poland)
Title: *Proteins and knots under tension*
Abstract: We highlight the diversity of mechanical clamps, some of them topological in nature, that have been found by making surveys of mechanostability of about 18 000 proteins within structure-based models. The existence of superstable proteins (with the characteristic unfolding force in the range of 1000 pN) is predicted. In these studies, mechanostabilityhas been assessed by stretching at constant speed. The focus of this lecture is stretching at constant tension - the case which is more relevant biologically. In particular, we find that proteins with knots unravel in a way similar to those without knots: there is a crossover between the inverse Gaussian distribution of unfolding times at high forces to the exponential distribution at low forces. However, we observe that sudden jumps in the extension of a protein do not necessarily lead to jumps in the location of the ends of the knot. We then propose a model to study the proteasome-induced protein translocatio. It involves constant-force pulling through a funnel-shaped potential. We find that a) the process of translocation unfolds proteins bound for degradtaion efficiently, b) the tension along the protein backbone is non-uniform, and c) the stalling force is smaller than the force of puling by the proteasomal motor. Our results provide insights into the mechanisms of unfolding used by biological unfoldases and indicate that the experimental paradigm used for measuring the traction power of the

proteasome.

Speaker: **Darcy, Isabel** (University of Iowa, USA)
Title: *Topology and structural self-organization in folded proteins*

Speaker: **Tetsuo, Deguchi** (Ochanomizu University, Tokyo, Japan)
Title: *Random knotting probability of DNA knots and scaling behavior*
Abstract: Random knots are created from the experiment of randomly closing the ends of nicked circular DNA. We evaluate random knotting probability for a very large number of knots by the simulation of self-avoiding polygons of cylindrical segments [1]. Here the radius of cylindrical segments corresponds to the thickness of screening due to counter ions in solution. We evaluate the knotting probabilities for various values of the screening radius. We show that a formula based on the scaling arguments gives good fitting curves to the knotting probability as a function of the number of segments of SAP. The formula is quite useful for composite knots, for which the knotting probability can be derived from those of constituent prime knots. We remark that the formula describes knotting probabilities for some finite numbers of segments, not for infnitely large numbers, although it is based on the scaling analysis which should be good for asymptotically large numbers of segments. Here we remark that finite-size effects are nontrivial in the scaling exponents of polymers [2].
Reference:
[1] E. Uehara and T. Deguchi, in preparation.
[2] E. Uehara and T. Deguchi, Exponents of intrachain correlation for self-avoiding walks and knotted self-avoiding polygons, J. Phys. A: Math. Theor. Vol. 46 (2013) 345001 (28pp).

Speaker: **Dietler, Giovanni** (Laboratoire de Physique de la Matière Vivante Institut de Physique des Systèmes Biologiques Ecole Polytechnique Fédérale de Lausanne, Lausanne Switzerland)
Title: *Sedimentation of macroscopic rigid knots and its relation to gel electrophoretic mobility of DNA knots*
Abstract: We address the general question of the extent to which the hydrodynamic behaviour of microscopic freely fluctuating objects can be reproduced by macrosopic rigid objects. In particular, we compare the sedimentation speeds of knotted DNA molecules undergoing gel electrophoresis to the sedimentation speeds of rigid stereolithographic models of ideal knots in both water and silicon oil. We find that the sedimentation speeds grow roughly linearly with the average crossing number of the ideal knot configurations, and that the correlation is stronger within classes of knots. This is consistent with previous observations with DNA knots in gel electrophoresis.
Work in collaboration with Cédric Weber, Mathias Carlen, Eric J. Rawdon & Andrzej Stasiak.

Speaker: **Claus, Ernst** (Western Kentucky University, USA)
Title: *The effect of confinement on knotting and geometry of random polygons*
Abstract: It is well known that genomic materials (long DNA chains) of living organisms are often packed compactly under extreme confining conditions using macromolecular self-assembly processes. It has been proposed that the topology of the packed DNA may be used to study the DNA packing mechanism. In this talk we introduce and study a model of equilateral random polygons confined in a sphere. This model is not meant to generate polygons that model DNA packed in a virus head directly. Instead, the average topological characteristics of this model may serve as benchmark data for totally randomly packed circular DNAs. The difference between the biologically observed topological characteristics and our benchmark data might reveal the bias of DNA packed in the viral capsids and possibly lead to a better understanding of the DNA packing mechanism, at least for the bacteriophage DNA. In more detail we consider equilateral random polygons of length n in a confinement sphere of radius R>1. In this talk we discuss how knotting probabilities and geometric properties of the random polygons change as a function of both n and R. Even for relatively small length (in our study we use polygons of a length up to 90 steps) such random polygons are knotted with very high probability - and the knots obtained are very complex (i.e. the knots have more than 16 crossings and cannot be identified).
Work in collaboration with Y. Diao, E Rawdon, U. Ziegler.

Speaker: **Haglund, Ellinor** (Center for Theoretical Biological Physics, University of California San Diego, USA)
Title: *Novel knotted structure*
Abstract: We discovered hidden complexity in the cysteine-knotted topology of the cytokine leptin characterized by a covalent loop (a so-called zero knot) where part of a terminus is slipknotted through the zero knot. We call this motif a Cysteine Knotted Helical Bundle (CKHB). Up to date, there have been no reports of four-helix bundles with similar threaded topology. We explored the question: Do other proteins contain similar CKHBs? We discovered 11 proteins with similar threaded topology. However, leptin is the only motif with a C-terminal zero knot whereas all other structures have an N-terminal zero knot. Structure-based models were used to in investigate the folding/threading mechanism for six four-helix bundles: four with a threaded topology and two unknotted cytokine homologs. We found that the order of events in folding of the four-helix-bundle is conserved and that the nucleation site for folding is the C-terminal helix. Leptin uses a variation of the same mechanism, but in a unique reversed order in which large structural components of the protein start out as part of the zero knot. This contrasts with the other four-helix bundles, which use large structural components as a scaffold for loop formation. Remarkably, leptin slipknots large structure parts through the C-terminal zero knot while the other CKHBs threads its C-terminal through the N-terminal zero knot like a thread through a needle (a so-called plugging mechanism). Conclusively, since four-helix bundles have similar functional and folding landscape it is important to point out that CHKBs with an N-terminal loop pin down the N-terminal helix (helix A), while leptin has the opposite zero knot, thus keeping the N-terminal dynamic. Crystal structures and modelling of receptor complexes reveals one conserved

interface (helix A interacting with the receptor) within the cytokines. This suggests a more dynamic assembly process between leptin and its receptor where the malleability of helix A could affect binding affinity and signaling.

Speaker: **Harris, Sarah** (Astbury Centre for Structural and Molecular Biology, University of Leeds, England)
Title: *Sequence Dependent Denaturation in Small DNA Circles: A Multiscale Approach*
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 and the stability of the duplex itself. At sufficiently high levels of negative supercoiling, the DNA is so destabilized that the duplex starts to denature, giving rise to a rich repertoire of structural defects whose biological importance is currently unknown. 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 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. However, even given the most powerful supercomputers currently available, we are unable to perform simulations over sufficiently long timescales to gain adequate statistics to quantify patterns of sequence dependent denaturation due to supercoiling. Consequently, in on going calculations we are comparing the results of the atomistic models with statistical mechanical methods [2] and coarse-grained simulations [3], which represent the DNA at the single base level.
[1] Du, Q., A. Kotlyar, and A. Vologodskii, Kinking the double helix by bending deformation. Nucleic Acids Research, 2008. 36: p. 1120-1128.
[2] Mitchell J. S., Laughton C. A. & Harris S. A. Atomistic simulations reveal bubbles, kinks and wrinkles in supercoiled DNA. Nucleic Acids Res. 2011. 39: p. 3928-3938.
[3] Šulc P., Romano F., Ouldridge T. E, Rovigatti L., Doye J. and Louis A. A. Sequencedependent thermodynamics of a coarse-grained DNA model. J. Chem. Phys. 2012, 137, 135101.
Work in collaboration with Thana Sutthibutpong, Christian Matek, Craig Benham, Gabriel Gouvea-Slade, Agnes Noy, Charlie Laughton, Elso Dringo, Jonathan Doye, Ard Loius.

Speaker: **Jackson, Sophie** (University of Cambridge, England)
Title: *Experimental studies on the folding pathways of knotted proteins*
Abstract: Since 2000, when they were first identified by Willie Taylor, the number of knotted proteins within the pdb has increased and there are now nearly 300 such structures. The polypeptide chain of these proteins forms a topologically knotted structure. There are now examples of proteins which form simple 3_1 trefoil knots, 4_1 , 5_2 Gordian knots and 6_1 Stevedore knots. Knotted proteins represent a significant

challenge to both the experimental and computational protein folding communities. When and how the polypeptide chain knots during the folding of the protein poses an additional complexity to the folding landscape.
We have been studying the structure, folding and function of two types of knotted proteins – the 3_1 -trefoil knotted methyltransferases and 5_2 -knotted ubiquitin C-terminal hydrolases. The first part of the talk will focus on our folding studies on knotted trefoil methyltransferases and will include our work determining the kinetic pathways by which such proteins fold, protein engineering studies which have created the deepest knotted protein structures known, experimental evidence for the retention of knots even in highly unstructured denatured polypeptide chains. In addition, recent work on the effect of molecular chaperones on the folding of these proteins, and new experimental evidence determining whether threading occurs from the N- or C-termini will be discussed.
The second part of the talk will focus on our studies of knotted ubiquitin C-terminal hydrolases – UCH-L1 and UCH-L3. Our work determining the folding pathways of these proteins will be presented, including recent unpublished work using NMR techniques to characterise the folding intermediates. The link between UCH-L1 and Parkinson's Disease will be discussed and the role of point mutations and oxidative damage on the structure of UCH-L1 will also be described.

Speaker: **Janse van Rensburg, Esaias J** (York University, Canada)
Title: *Modelling the Entropic Pressure near a Ring Polymer*
Abstract: The entropic pressure in the vicinity of a ring polymer in a good solvent is modelled in the square and cubic lattices by sampling lattice polygons using a Monte Carlo method. I shall explain the scaling of the pressure and present numerical data confirming the scaling analysis in the square lattice. In addition, some preliminary results for the pressure near lattice polygons attached to a hard wall will be presented in the square and cubic lattices. In three dimensions these polygons can be knotted, and that will have an effect on the pressure. Joint work with Farid Gassoumov.

Speaker: **Kadomatsu Hermosa, Maridian José** (National University of Asuncion, San Lorenzo, Paraguay)
Title: *Maxwell-Stefan electrophoresis simulation of equal mass type A catenanes and supercoiled dimers*
Abstract: The analysis of two topological DNA families, type A catenanes (CatAs) and supercoiled dimers (Dims) of a bacterial plasmid by two-dimensional agarose gel electrophoresis (2Dgels) was used to show that the number of crossings is not the only variable that determines electrophoretic mobility in agarose gels run under different conditions. To find out other parameters that could explain these differences in mobility, we consider DNA in the gel as a two-phase fluid model in a porous media, using conservation law models for the mass and the Maxwell-Stefan equation as a constitutive relation between the velocity of topoisomers and the electrostatic gradient of the electrophoresis experiment. The velocity of topoisomers was obtained experimentally considering velocity as a function of the electrophoretic variables. From the modeling, a nonlinear hyperbolic partial differential equation was obtained which was subsequentially

solved using a Lax-Friedrich finite difference scheme. Comparisons between experimental 2Dgels and simulations showed that the number of crossing was not the only determinant factor affecting mobility and indicated that molecular deformability also played a crucial role. This observation explains the differences in electrophoretic mobility experimentally observed for CatAs and Dims of the same mass. The numerical results also showed that the drag force of ions in the buffer has a strong influence in the velocity of topoisomers. The results obtained so far encouraged us to improve the modeling as well as to develop faster numerical schemes.
This work was partially supported by CONACyT-Paraguay and Spanish BFU2011-22489. Work in collaboration with Maridian J. Kadomatsu-Hermosa, Jorge Cebrián, María José Fernández-Nestosa, Christian E. Schaerer, Dora B. Krimer and Jorge B. Schvartzman

Speaker: **Li, Hongbin** (University of British Columbia, Vancouver, Canada)
Title: *Mechanically Tightening a Protein Slipknot into a Trefoil Knot*
Abstract: Knotted polypeptide chain is one of the most surprising topological features found in some proteins. How knotted proteins overcome the topological difficulty to fold into their native three dimensional structures proteins has become a challenging problem. It was suggested that a structure of slipknot could serve as an important intermediate state during the folding of knotted proteins. Here we use single molecule force spectroscopy (SMFS) as well as steered molecular dynamics (SMD) simulations to investigate the mechanism of transforming a slipknot protein AFV3-109 into a tightened trefoil knot by pulling. Our results show that by pulling the N-terminus and the threaded loop of AFV3-109, the protein can be unfolded via multiple pathways and the slipknot can be transformed into a tightened trefoil knot, which involves ~13 amino acid residues. SMD simulation results, which are consistent with our experimental findings, provide a detailed molecular mechanism of mechanical unfolding and knot tightening of AFV3-109. SMD simulations reveal that interactions between β-strands on the threading loop and knotting loop that are sheared during stretching provide high mechanical resistance in the process of forming the trefoil knot, i.e., pulling threaded loop through knotting loop.

Speaker: **Micheletti, Cristian** (International School for Advanced Studies, Italy)
Title: *Dynamical aspects of entangled chains*
Abstract: The presence of physical knots in linear chains can impact significantly their metric, mechanical and also dynamical properties. We shall discuss two examples which illustrate the relationship between chain kinetics and entaglement. Specifically, we shall first consider the spontaneous tying and untying of knots in equilibrated linear chains and discuss it in connection with the mechanisms that are arguably responsible for the appearance of knots in flexible biomolecules. Next we shall discuss the case of knotted polyeletrolyte chains that are driven through a nanopore by an electric field. It is shown that the presence of knots do not per se cause the translocation process to jam. Rather, knots introduce an effective friction that increases with the applied force, and practicallyhalts the translocation above a threshold force.

Speaker: **Millett, Kenneth** (University of California, Santa Barbara, USA)
Title: *Resolving Knotting Complexity in Proteins and Tight Topological Knots*
Abstract: Employing the MDS analysis, one defines the knot type of open chains thereby providing a basic tool in the study of fine –grained knotting structure in proteins (or other open chains) as well as classical topological knots (for example tight knots). The resulting matrix of data arising from the entire collection of sub chains is represented as a triangular or circular knotting fingerprint. From the knotting regions one derives an oriented graph from whose characteristic structure one can derive characteristics of the complexity of the knotting and the knotting pathways associated to the given protein structure or the specific tight knot type.
This is joint research with Henrich, Hyde, Rawdon, and Stasiak.

Speaker: **Minor, Wladek** (University of Virginia, Charlottesville, USA)
Title: *Experiment and modeling: competitive or complementary approaches to structural biology?*
Abstract: The three-dimensional structures determined by X-ray crystallography play a central role in understanding protein-small molecule and protein-protein interactions at the molecular level. Each unique structure deposited to the Protein Data Bank (PDB) increase the number of models that can be calculated (predicted) for experimentally unknown structures. The experimental verification of models produced by the CASP competition shows that top experts can accurately predict the overall structure of proteins when there is a similar protein of known structure and in some cases even when a protein is not similar to any protein with a known structure. However, the experimental verification of applicability of automatic methods developed for meta-servers shows that the accuracy of a predicted model significantly drops when the sequence similarity between the model and an experimentally derived structure drops below 30%.
Protein 3-D structures have long been used to search for new drug targets, but only a fraction of new drugs coming to the market were developed with the use of structure-based drug discovery method. The '*in silico*' screening of potential ligands is much less successful than prediction of native protein structures. The combined approach of multidisciplinary experimental and computational methods will lead to a dramatic increase of accuracy of computational screening. Thus our understanding of protein-ligand and protein-protein interactions and our understanding of the molecular foundation of human diseases and thus leading to a high-output structure-based drug discovery system.

Speaker: **Nicodemi, Mario** (Universita' di Napoli, Italy)
Title: *Models of chromatin spatial organisation in the cell nucleus*
Abstract: In the cell nucleus chromosomes have a complex architecture serving vital functional purposes. Recent experiments have started unveiling the interaction map of DNA sites genome-wide, revealing different levels of organisation at different scales. The principles, though, which orchestrate such a complex 3D structure remain still mysterious. I will give an overview of the picture emerging from classical polymer

physics of some general aspect of chromatin spatial organisation. The available experimental data, which can be rationalised in a single framework, support a picture where chromatin is a complex mixture of differently folded regions, self-organised across spatial scales according to basic physical mechanisms. I will also discuss applications to specific DNA loci, where models informed with biological details are tested against targeted experiments.
Work in collaboration with M. Barbieri, M. Chotalia, L.M. Lavitas, J. Fraser, J. Dostie, A. Pombo.

Speaker: **Onuchic, Jose** (Rice University, Houston, USA)
Title: *Knotting proteins in implicit solvent*

Speaker: **Panagiotou, Eleni** (University of California, Santa Barbara, USA)
Title: *Entanglement in systems of curves with Periodic Boundary Conditions*
Abstract: Periodic Boundary Conditions (PBC) are often used for the simulation of complex physical systems of open and closed curve models of polymers or vortex lines in a fluid flow. Using the Gauss linking number, we define the periodic linking number as a measure of entanglement for two oriented curves in a system employing PBC. In the case of closed curves in PBC, the periodic linking number is a topological invariant that depends on a finite number of components in the periodic system. For open curves, the periodic linking number depends upon the entire infinite system and we prove that it converges to a real number that varies continuously with the configuration. Finally, we define two cut-offs of the periodic linking number and we compare these measures when applied to a PBC model of polyethylene melts.

Speaker: **Plotkin, Steven** (University of British Columbia, Vancouver, Canada)
Title: *From Euclidean distance, to polymer uncrossing and knotting, to protein folding rate prediction*
Abstract: A fundamental problem of relevance to protein folding and structural comparison of biomolecules is the notion of what *distance* means for higher-dimensional objects such as a polymer. Here we generalize the notion of distance between points to distance between non-crossing space curves to uniquely define the Euclidean distance between two biopolymer conformations. We apply this order parameter to the problem of protein folding rates and reaction coordinates. To do so, we develop a method for generating a diverse conformational ensemble, to characterize properties of the unfolded states of intrinsically disordered or intrinsically folded proteins. We find that for a randomly selected dataset of 15 non-homologous 2- and 3-state proteins, quantities such as the average root mean squared deviation between the folded structure and unfolded ensemble correlate with folding rates as strongly as absolute contact order. In an all-atom representation that respects steric constraints, the distance travelled per residue naturally partitions into a smooth “laminar” and subsequent “turbulent” part of the trajectory. This latter conceptually simple measure with no fitting parameters predicts folding rates in 0 M denaturant with remarkable accuracy ($r = -0.95$, $p = 1e-7$). The high correlation between folding times and sterically modulated,

reconfigurational motion supports the rapid collapse of proteins prior to the transition state as a generic feature in the folding of both two-state and multi-state proteins. This method for generating unfolded ensembles provides a powerful approach to address various questions in protein evolution, misfolding and aggregation, transient structures, and molten globule and disordered protein phases.

Speaker: **Schvartzman, Jorge** (Centro de Investigaciones Biológicas, Madrid, España)
Title: *DNA dynamics during replication: the benefit of entanglement*
Abstract: During replication, DNA molecules undergo topological changes that affect supercoiling, catenation and knotting. To better understand this process and the role of topoisomerases, the enzymes that control DNA topology *in vivo*, high resolution two-dimensional agarose gel electrophoresis (2Dgels) and atomic force microscopy (AFM) were used to examine partially replicated bacterial plasmids containing replication forks stalled at specific sites. The exposure of these replication intermediates (RIs) isolated from *Escherichia coli* mutant cells proficient or deficient for Topo IV to various topoisomerases *in vitro* generated surprising observations. The results obtained together with computer simulations based on Metropolis Monte Carlo helped us to predict the thermodynamic stability of the molecules and to determine the potential energy that can be stored in the replicated and unreplicated regions. Altogether, these observations strongly suggest that type II DNA topoisomerases recognize the geometry of DNA duplex crossings, probably throughout their interaction with other proteins. The geometry of the crosses differs between the unreplicated and replicated regions, changes continuously as replication forks advance and is dramatically altered by deproteinization.
Work in collaboration with Jorge Cebrián ,Víctor Martínez, María José Fernández, Christian Schaerer, Pablo Hernández, Dora B. Krimer, Jorge B. Schvartzman.

Speaker: **Shimokawa, Koya** (Saitama University, Japan)
Title: *FtsK-dependent XerCD-dif recombination unlinks replication catenanes in a stepwise manner*
Abstract: In Escherichia coli, complete unlinking of newly replicated sister chromosomes is required to ensure their proper segregation at cell division. While replication links are removed primarily by topoisomerase IV (TopoIV), XerCD-dif site-specific recombination can mediate sister chromosome unlinking in TopoIV-deficient cells. This reaction is activated at the division septum by the DNA translocase FtsK, which coordinates the last stages of chromosome segregation with cell division. It has been proposed that, after being activated by FtsK, XerCD-dif recombination removes DNA links in a stepwise manner. Here we provide a mathematically rigorous characterization of this topological mechanism of DNA unlinking. We show that stepwise unlinking is the only possible pathway that strictly reduces the complexity of the substrates at each step. Finally, we propose a topological mechanism for this unlinking reaction.
This is a joint work with: Kai Ishihara, Ian Grainge, David J. Sherratt, and Mariel Vazquez.

Speaker: **Soteros, Chris** (University of Saskatchewan, Canada)
Title: *Entanglement complexity of compressed and stretched polygons in lattice tubes*
Abstract: Self-avoiding walks and polygons are the standard statistical mechanics lattice model of linear and ring polymers in dilute solution. These models have also proven to be useful for investigating questions about DNA topology as well as about confined polymers. In this talk I will review transfer-matrix results regarding the entanglement complexity of self-avoiding polygon models in infinite lattice tubes in order to understand the effects of confinement on ring polymer entanglement. New theoretical and numerical results will be discussed regarding polygons under a tensile force as well as maximally compressed polygons in the tube.

Speaker: **Stasiak, Andrzej** (Center for Integrative Genomics, University of Lausanne, Switzerland)
Title*: Models that include supercoiling of topological domains reproduce several known features of interphase chromosomes*
Abstract: Understanding the structure of interphase chromosomes is essential to elucidate regulatory mechanisms of gene expression. During recent years, high-throughput DNA sequencing expanded the power of chromosome conformation capture (3C) methods that provide information about reciprocal spatial proximity of chromosomal loci. Since 2012 it is known that entire chromatin in interphase chromosomes is organized into regions with strongly increased frequency of internal contacts. These regions, with the average size of about 1Mb were named topological domains. More recent studies demonstrated presence of unconstrained supercoiling in interphase chromosomes. Using Brownian dynamics simulations, we show here that by including supercoiling into models of topological domains one can reproduce and thus provide possible explanations of several experimentally observed characteristics of interphase chromosomes, such as their complex contact maps, for example.
Work in collaboration with Fabrizio Benedetti, Julien Dorier, Yannis Burnier.

Speaker: **Sumners, DeWitt** (Florida State University, Tallahassee, USA)
Title: *Reconnection In Biology and Physics*
Abstract: Reconnection is an important event in many areas of science, including site-specific DNA recombination and the reconnection of field lines in astro- and plasma physics. We will discuss the conservation of writhe in a reconnection, and the behavior of twist in site-specific DNA recombination. Using the theorem of Moffatt and Ricca (Proc. Roy. Soc. 1992), the helicity of a magnetic flux tube can be calculated in terms of the writhe of the centerline and the twist of the ribbon determined by the centerline and one of the other field lines in the flux tube tube. This talk will present the proof of the following:
Theorem: Given a reconnection event between a pair of magnetic flux tubes of identical flux, suppose that the twist of the reconnected tube is the sum of the twists of the individual tubes. Then helicity is conserved by the reconnection event — the helicity of the reconnected flux tube is the sum of the helicities of the individual tubes. Any deviation from helicity conservation is entirely due to twist inserted locally at the

reconnection site (the writhe component of helicity is always conserved).
This is joint with Christian Laing and Renzo Ricca.

Speaker: **Szafron, Michael** (University of Saskatchewan, Saskatoon, Canada)
Title: *Asymptotics of the length of an essential arc in a simple-cubic-lattice model for strand-passage*
Abstract: DNA experiments demonstrate that Type II topoisomerases unknot and unlink DNA in preparation for cellular processes such as replication, but how the enzyme identifies a "knotted region", from which it selects a site to act, remains an open problem. To study this problem, a measure for determining the "knotted region" is required. In this presentation, a new measure for the length of a knotted region in a "pinched" self-avoiding polygon (SAP) in simple cubic lattice will be presented and some asymptotic properties of this measure will be discussed.

Speaker: **Szymczak, Piotr** (Institute of Theoretical Physics, University of Warsaw, Poland)
Title: *Translocating knotted peptides*
Abstract: In recent years a surge of interest has arisen in properties and function of knotted proteins. As more and more knotted structures are discovered in the Protein Data Bank, it becomes increasingly important to understand how, if at all, the non-trivial topology affects the protein's function in the cell. In particular, it has been hypothesized that the presence of a knot in the polypeptide backbone may affect the ability of knotted proteins to be degraded in proteosome or translocated through the intercellular membranes, e.g. during import into mitochondria. In these processes, the translocating proteins typically have to pass through constrictions that are too narrow to accommodate folded structures, thus translocation must be coupled to protein unfolding. However, as shown in a number of theoretical and experimental studies the protein knots get tightened under the tension. The radius of gyration of the tight knot is about 7-8 Angstrom, whereas the diameters of the narrowest constriction of the mitochondrial pores are in the 12-15 Angstrom range, making it possible for the knots to get stuck during the translocation process. We report the result of molecular dynamics simulations of knotted protein translocation which show how such topological traps might be prevented by using a pulling protocol of a repetitive, on-off character. Such a repetitive pulling is biologically relevant, since the mitochondrial import motor, like other ATPases transform chemical energy into directed motions via nucleotide-hydrolysis-mediated conformational changes, which are cyclic in character.

Speaker: **Vazquez, Mariel** (San Francisco State University, USA)
Title: *DNA unlinking by Xer recombination*
Abstract: Newly replicated circular chromosomes are topologically linked. XerCD-*dif*-FtsK recombination acts in the replication termination region of the *Escherichia coli* chromosome to remove links introduced during homologous recombination and replication, whereas Topoisomerase IV removes replication links only. Based on gel mobility patterns of the products of recombination, a stepwise unlinking pathway has

been proposed. We show definitively that there is a unique shortest pathway of unlinking by XerCD-*dif*-FtsK that strictly reduces the complexity of the links at every step. We delineate the mechanism of action of the enzymes at each step along this pathway and provide a 3D interpretation of the results.
This is joint work with Koya Shimokawa, Kai Ishihara, Ian Grainge and David Sherratt.

Speaker: **Viranu, Peter** (Johannes Gutenberg University Mainz, Germany)
Title: *Molecular simulations of knotted proteins and DNA*
Abstract: After providing a short introduction to knotted proteins and showing a few novel structures, I will present simulations of a coarse-grained heteropolymer model and argue that the addition of a single degree of freedom (in this case sequence) may facilitate evolution towards unknotted proteins. I will also present a mechanism which allows two knots on a polymer chain to pass through each other and swap positions along the strand. Associated "topological" free energy barriers only amount to a few kT, which may enable the interchange of knots on a single DNA molecule.

Speaker: ***Whittington, Stu*** (University of Toronto, Canada)
Title: *Entanglements in self-avoiding walks: Old wine in new bottles*
Abstract: Although it is straightforward to define knotting in simple closed curves, this is not so easy in open curves. What do we mean by self-entanglements in linear polymers? We shall describe some of the ideas that have been used to capture these entanglements, compare their relative advantages and disadvantages, and show that different approaches can give very different results. Finally we shall argue that, if the curve is badly entangled, all of the approaches work reasonably well.