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Volume 150

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Fadil Santosa, Director of the IMA

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Craig John Benham · Stephen Harvey · Wilma K.
Olson · De Witt L. Sumners · David Swigon
Editors

Mathematics of DNA Structure, Function and Interactions

Springer

Editors

Craig John Benham
Department of Mathematics
University of California
451 E. Health Sciences Drive
Davis CA 95616
GBSF
USA
http://genomics.ucdavis.edu/benham/
benham.php

Stephen Harvey
Department of Chemistry and Biochemistry
Georgia Institute of Technology
Atlanta GA 30332-0400
USA
http://www.chemistry.gatech.edu/faculty/Harvey/

Wilma K. Olson
Department of Chemistry
   and Chemical Biology
Rutgers University
610 Taylor Rd.
Piscataway NJ 08854-8087
USA
http://rutchem.rutgers.edu/content_
dynamic/faculty/wilma_k_olson.shtml

De Witt L. Sumners
Department of Mathematics
Florida State University
Tallahassee FL 32306-4510
208 Love Bldg.
USA
http://www.math.fsu.edu/~sumners/

David Swigon
Department of Mathematics
University of Pittsburgh
301 Thackeray Hall
Pittsburgh PA 15260
USA
http://www.math.pitt.edu/~swigon/

FOREWORD

This IMA Volume in Mathematics and its Applications

MATHEMATICS OF DNA STRUCTURE, FUNCTION, AND INTERACTIONS

contains papers presented at a highly successful one-week workshop held on September 16-21, 2007 on the same title. The event was an integral part of the 2007–2008 IMA Thematic Year on "Mathematics of Molecular and Cellular Biology." We are grateful to all the participants for making this workshop a very productive and stimulating event.

We owe special thanks to Craig John Benham (Davis Genome Center, University of California, Davis), Stephen Harvey (Department of Chemistry and Biochemistry, Georgia Institute of Technology), Wilma K. Olson (Department of Chemistry and Chemical Biology, Rutgers University), De Witt L. Sumners (Department of Mathematics, Florida State University), and David Swigon (Department of Mathematics University of Pittsburgh) for their superb role as workshop organizers and editors of these proceedings.

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Series Editors

Fadil Santosa, Director of the IMA

Markus Keel, Deputy Director of the IMA

PREFACE

Propelled by the success of the sequencing of the human and many related genomes, molecular and cellular biology has delivered significant scientific breakthroughs. Mathematics (broadly defined) continues to play a major role in this effort, helping to discover the secrets of life by working collaboratively with bench biologists, chemists and physicists. The critical need, which has already begun, is the development of a quantitative body of theory for biology. This development of theory is expected to have the same impact on biology as it did on the sciences of physics, chemistry and engineering in the 20th century. People with strong backgrounds in both biology and the mathematical sciences are creating this quantitative body of theory. Because of its outstanding record of interdisciplinary research and training, the IMA was an ideal venue for the 2007-2008 IMA thematic year on Mathematics of Molecular and Cellular Biology. This volume is dedicated to the memory of Nicholas Cozzarelli, a dynamic leader who fostered research and training at the interface between mathematics and molecular biology. Nick was the founding director of the Program in Mathematics and Molecular Biology (PMMB), a national research and training consortium in existence from 1987-2007. Two of the editors of this volume (Olson and Sumners) were members of PMMB, and one of the editors (Swigon) was a PMMB Fellow. Seven of the thirty-one authors of papers in this volume were PMMB Fellows, an indication of the influence of Nick Cozzarelli on research at the mathematics/molecular biology interface. The kickoff event for the IMA thematic year was the IMA tutorial on Mathematics of Nucleic Acids, and the following 6-day IMA workshop Mathematics of DNA Structure, Function and Interactions, held during September 15-21, 2007 in Minneapolis. The workshop consisted of 32 talks and 17 posters, and enjoyed participation by 120 interdisciplinary scientists, a mix of mathematicians, biologists, chemists, physicists and engineers. This volume consists of a remembrance of Nick Cozzarelli by two past members of his Berkeley molecular biology laboratory, and 15 papers contributed by speakers at the tutorial and workshop. It contains of some of the state-of-the-art in mathematical approaches to DNA as of September 2007. A short description of the articles in the volume follows. For a more complete idea of the content of each article, please see the introductions to each article.

1. Nick Cozzarelli: A personal remembrance by Stephen D. Levene and Lynn Zechiedrich. Steve and Lynn were postdocs in the Cozzarelli lab during the period 1989-1997. This remembrance is very perceptive in the description of Cozzarelli as a blast-ahead interdisciplinary scientist, and recounts a hilarious incident at the lab in which Nick accepts an unexpected NIH merit award over the phone.

2. Mathematical methods in DNA topology: Applications to chromosome organization and site-specific recombination, by Javier Arsuaga, Yuanan Diao, and Mariel Vazquez. This paper explores some of the uses of knot theory and 3-dimensional manifold topology to model chromosome organization and the binding and mechanism of site-specific DNA recombination enzymes. The paper reviews both theoretical and computational topological methods.

3. Conformational statistics of DNA and diffusion equations on the Euclidean group by Gregory S. Chirikjian. Using wormlike chain models for DNA, this paper studies the problem of determining the probability density of end-to-end chain position and orientation. Solutions are obtained by solving the Fokker-Planck equation that describes a diffusion process on the Euclidean motion group.

4. Perspectives on DNA looping, by Laura Finzi. This paper presents a survey of the field of DNA looping, with emphasis on three repressor systems lac, gal and phage lambda. The paper concentrates on the insight gained on transcriptionally-relevant DNA looping mechanisms by single-molecule approaches.

5. Differences between positively and negatively supercoiled DNA that topoisomerases may distinguish, by Jonathan M. Fogg, Daniel J. Catanese, Jr. Graham Randall, Michelle C. Swick, and Lynn Zechiedrich. This article presents a new biological perspective on DNA supercoiling, including a review of the functional importance and practical issues encountered in laboratory work. It provides hints of the features of DNA structure and energetics that topoisomerases may utilize in controlling the supercoiled state of DNA.

6. Calibration of tethered particle motion experiments, by Lin Han, Bertrand Lui, Seth Blumberg, John F. Beausang, Philip C. Nelson, and Rob Phillips. The Tethered Particle Motion (TPM) method has been used to observe and characterize a variety of protein-DNA interactions including DNA looping and transcription. This paper describes a detailed calibration of TPM magnitude as a function of DNA length and particle size, exploring how experimental parameters such as acquisition time and exposure time affect the apparent motion of the tethered particle

7. Difference topology: Analysis of high-order DNA-protein assemblies, by Makkuni Jayaram and Rasika Harshey. This paper studies Difference topology, a method for deciphering the DNA topology within DNA-protein complexes that are not readily amenable to standard structural analyses. The logic is to trap the crossings formed by distinct DNA segments by tying them into knots or links by site-specific DNA inversion and deletion, respectively, carried out by a recombinase. The number of such crossings can then be counted by analytical methods such as gel electrophoresis or electron microscopy.

8. Useful intrusions of DNA topology into experiments on protein-DNA geometry, by Jason D. Kahn, James R. Jenssen, and Vasavi Vittal.

This paper studies the use of small DNA minicircles to characterize protein-induced DNA bending and twisting. In every case studied, topological characterization of minicircle synthesis or properties has led to unexpected geometric or mechanistic conclusions.

9. Topological analysis of DNA-protein complexes, by Soojeong Kim and Isabel K. Darcy. Tangles have been used to model protein-bound DNA. The protein is represented by a 3D ball and the protein-bound DNA is represented by the strings embedded in the 3D ball. This paper reviews tangle analysis of protein-DNA complexes involving three or four segments of DNA.

10. Closing the loop on protein-DNA interactions: Interplay between shape and flexibility in nucleoprotein assemblies having implications for biological regulation, by Stephen D. Levene and Yongli Zhang. The formation of DNA loops by proteins bound at distant sites along a single molecule is an essential mechanistic aspect of many biological processes including gene regulation, DNA replication, and recombination. This paper describes a rigorous theory for DNA loop formation that connects the global mechanical and geometric properties of both DNA and protein, with applications to the problem of loop-mediated gene repression in vivo by lac repressor.

11. Four-way helical junctions in DNA molecules, by David M.J. Lilley. Four-way (Holliday) junctions are branch points in DNA where four helices are interconnected by the mutual exchange of strands. This paper presents a short review focusing on recent developments in understanding the structure and dynamics of DNA four-way junctions.

12. Micromechanics of single supercoiled DNA molecules, by John F. Marko. This paper reviews the theory of the mechanical response of single DNA molecules under stretching and twisting stresses. Using established results for the semiflexible polymer including the effect of torsional stress, and for the free energy of plectonemic supercoils, a theory of coexisting plectonemic and extended DNA is constructed and shown to produce phenomena observed experimentally.

13. Flexibility of nucleosomes on topologically constrained DNA, by Andrei Sivolob, Christophe Lavelle and Ariel Prunell. This paper reviews results on nucleosome conformational flexibility, its molecular mechanism and its functional relevance. The initial approach combined both empirical measurement and theoretical simulation of the topological properties of single particles reconstituted on DNA minicircles.

14. The mathematics of DNA structure, mechanics, and dynamics, by David Swigon. A brief review is given of the main concepts, ideas, and results in the fields of DNA topology, elasticity, mechanics and statistical mechanics. Discussion includes the notions of the linking number, writhe, and twist of closed DNA, elastic rod models, sequence-dependent base-pair level models, statistical models such as helical worm-like chain and freely jointed chain, and dynamical simulation procedures.

15. Paradox regained: A topological coupling of nucleosomal DNA wrapping and chromatin fibre coiling, by Andrew Travers. The folding and unfolding of the chromatin fibre is a fundamental control point for the regulation of eukaryotic transcription. This paper presents a novel solution to the so-called linking number paradox problem and shows that this solution implies that the chromatin fibre acts a tunable coil.

16. Statistical-mechanical analysis of enzymatic topological transformations in DNA molecule, by Alexander Vologodskii. This paper reviews computational approaches to the analysis of action of two classes of DNA enzymes: topoisomerase and recombinase. Comparing the simulated distribution with corresponding experimental data serves as a model test. The major principles and assumptions of the approach, which is based on the simulation of an equilibrium set of DNA conformations, are discussed.

On behalf of the editors, I would like to thank the authors of papers for contributing to this volume, and for their cooperation in the editorial process. Special thanks go to Patricia V. Brick and Dzung N. Nguyen for their excellent assistance in preparing papers for the volume publisher.

Craig John Benham
Department of Mathematics
University of California, Davis
http://genomics.ucdavis.edu/benham/benham.php

Stephen Harvey
Department of Chemistry and Biochemistry
Georgia Institute of Technology
http://www.chemistry.gatech.edu/faculty/Harvey/

Wilma K. Olson
Department of Chemistry and Chemical Biology
Rutgers University
http://rutchem.rutgers.edu/content_dynamic/faculty/wilma_k_olson.shtml

De Witt L. Sumners
Department of Mathematics
Florida State University
http://www.math.fsu.edu/~sumners/

David Swigon
Department of Mathematics
University of Pittsburgh
http://www.math.pitt.edu/~swigon/

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