# Architecture of Eukaryotic Genes

Edited by G. Kahl

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Editor:
Prof. Dr. Günter Kahl
Fachbereich Biologie
Pflanzliche Molekularbiologie
Johann Wolfgang Goethe-Universität
Siesmayerstraße 70
D-6000 Frankfurt am Main 11

*Cover illustration*: Cromatin network of a cell nucleus (left), higher order structures of chromatin (middle) and nucleosomal arrays (right). Photo and preparation: Dr. H. Zentgraf, DKFZ Heidelberg, Institut für Virusforschung, Im Neuenheimer Feld.280, D-6900 Heidelberg, Federal Republic of Germany.

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# Preface

Over the past decade, the enormous development of recombinant DNA technology and the resulting explosive growth in DNA sequence data have considerably promoted our understanding of the primary structure of eukaryotic genes. Though the linear array of bases within a gene and its regulatory sequences reveals their identity, coding qualities and potential functi[illegible], [illegible]mportance for the switching-on and switching-off of genes is very limited. The actual function of a gene is directed by its three-dimensional arrangement within its "chromatin" environment, where "chromatin" describes the specific association of nuclear proteins with the various topological forms of DNA. Imposed on the primary sequence of DNA, this architecture is a result of various DNA conformations, specific DNA-protein- and protein-protein-interactions and their gross or subtle changes in response to intrinsic or environmental stimuli. In essence, a deeper understanding of how eukaryotic genes function *in vivo* depends on a most detailed and complete knowledge of how the chromatin architecture around these genes is arranged, altered and rearranged.

Though considerable progress has been made in various fields of chromatin research in its broadest sense, no single treatise has yet been dedicated to a synopsis of all aspects of this extremely complex nuclear structure. The present book aims at filling this gap, and covers an enormous spectrum of topics. Its strength lies in the fact that experts with international reputation have highlighted current research in their field and presented an overview on most aspects of the statics and dynamics of chromatin architecture. The weakness of such a book inevitably lies in its advice to the reader to piece together the mosaics for a yet incomplete picture by himself. Clearly some aspects would have deserved more detailed treatment, in some cases a seperate chapter. In spite of these, and maybe other insufficiences as well, the various authors have striven to present not only excellent up-to-date reference texts but have also presented highlights from the forefront of current research. Extended bibliographies allow the reader to pursue specific topics in greater depth.

Since this book is based on a symposium on chromatin structure of plant genes organized by the editor in 1986, it included work both on animal or human and plant chromatin, so that direct comparisons of this structure from different kingdoms can be made. It is the hope of the editor that this should encourage the exchange of ideas between scientists from both fields.

Although aware of the fact that the contributions cannot adequately describe the complex gene architecture in toto, I nevertheless address the book to those students who wish to become acquainted with or involved in the current research on chromatin architecture, and to those colleagues who are already engaged in this area of molecular biology, but still miss such an overview. It can be expected that the study of the architecture of eukaryotic genes will considerably expand our knowledge in this important field of molecular biology.

Frankfurt, September 1987 Günter Kahl

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# List of Contributors


Amero, S.A.
Department of Microbiology
University of Virginia, School of Medicine
Charlottesville, Virginia 22908
USA
(Chapter 9)

Ashraf, M.
Laboratory of Plant Cell and Molecular Biology
University of Florida
Gainesville, Florida 32611
USA
(Chapter 20)

Bollinger, S.
Laboratory of Plant Cell and Molecular Biology
University of Florida
Gainesville, Florida 32611
USA
(Chapter 20)

Bonner, J.
Division of Biology
California Institute of Technology
Pasadena, California 91125
USA
(Chapter 28)

Borgmeyer, U.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 17)

Bustin, M.
Laboratory of Molecular Carcinogenesis
National Cancer Institute
National Institutes of Health
Bethesda, Maryland
USA
(Chapter 8)

Cantor, C.R.
Department of Genetics and Development
College of Physicians and Surgeons
Columbia University
701 West 168th Street
New York, New York 10032
USA
(Chapter 27)

Cartwright, I.L.
Department of Biochemistry and Molecular Biology
University of Cincinnati College of Medicine Cincinnati,
Ohio 45267-0522
USA
(Chapter 14)

Doenecke, D.
Institut für Biochemie
Universität Göttingen
Humboldt-Allee 23
D-3400 Göttingen
Federal Republic of Germany
(Chapter 5)

Doerfler, W.
Institut für Genetik
Universität Köln
D-5000 Köln
Federal Republic of Germany
(Chapter 21)

Drahovsky, D. (deceased June 21, 1987)
Zentrum der Biologischen Chemie
Universität Frankfurt
D-6000 Frankfurt/Main
Federal Republic of Germany
(Chapter 23)

Elgin, S.C.R.
Department of Biology
Washington University
St. Louis, Missouri 63130
USA
(Chapters 9 and 14)

Elliston, K.
Waksman Institute, Rutgers
The State University of New Jersey
Piscataway, New Jersey 08854-0759
USA
(Chapter 2)

Ferl, R.J.
Laboratory of Plant Cell and Molecular Biology
University of Florida
Gainesville, Florida 32611
USA
(Chapter 20)

Flavell, R.B.
Department of Molecular Genetics
Plant Breeding Institute
Cambridge CB2 2LQ
England
(Chapter 19)

Fritton, H.P.
Institut für Physiologische Chemie,
Physikalische Biochemie und Zellbiologie
Universität München
Schillerstr. 44
D-8000 München 2
Federal Republic of Germany
(Chapter 16)

Ganal, M.
Institut für Biologie II
Lehrstuhl Genetik
Universität Tübingen
Auf der Morgenstelle 28
D-7400 Tübingen
Federal Republic of Germany
(Chapter 18)

Gasser, S.M.
Swiss Institute for Experimental Cancer Research
Chemin des Boveresses 155
1066 Epalinges s/Lausanne
Switzerland
(Chapter 25)

Gerstner, J.
Institut für Biologie II
Lehrstuhl Genetik
Universität Tübingen
Auf der Morgenstelle 28
D-7400 Tübingen
Federal Republic of Germany
(Chapter 18)

Gigot, C.
Institut de Biologie Moleculaire des
Plantes (IBMP)
CNRS
12 rue du Général Zimmer
67000 Strasbourg Cedex
France
(Chapter 10)

Görz, A.
Fachbereich Biologie
Molekulare Pflanzenbiologie
Universität Frankfurt/Main
D-6000 Frankfurt/Main
Federal Republic of Germany
(Chapter 15)

Goodwin, G.
Institute of Cancer Research
Chester Beatty Laboratories
Fulham Road
London SW3 6JB
England
(Chapter 8)

Gruenbaum, Y.
Department of Genetics
Institute of Life Sciences
The Hebrew University
Jerusalem 91904
Israel
(Chapter 26)

Grussenmeyer, T.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 17)

Hatzopoulos, A.K.
Max-Planck-Institut für Biophysikalische Chemie
D-3400 Göttingen
Federal Republic of Germany
(Chapter 4)

Hecht, A.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 17)

Hemleben, V.
Institut für Biologie II
Lehrstuhl Genetik
Universität Tübingen
Auf der Morgenstelle 28
D-7400 Tübingen
Federal Republic of Germany
(Chapter 18)

Hepburn, A.G.
Department of Agronomy
University of Illinois
1102 S. Goodwin Avenue
Urbana, Illinois 61801
USA
(Chapter 22)

Herrera, R.E.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg
Federal Republic of Germany
(Chapter 1)

Hirasawa, E.
Osaka City University
Faculty of Science
Sumiyoshu-ku, Sugimoto-cho
Osaka 558
Japan
(Chapter 15)

Hochstrasser, M.
Department of Biology
Massachusetts Institute of Technology
77 Massachusetts Avenue
Cambridge, Massachusetts 02139
USA
(Chapter 26)

Hörz, W.
Institut für Physiologische Chemie,
Physikalische Biochemie und Zellbiologie
Universität München
Goethestr. 33
D-8000 München 2
Federal Republic of Germany
(Chapter 12)

Hoeveler, A.
Institut für Genetik
Universität Köln
D-5000 Köln
Federal Republic of Germany
(Chapter 21)

Igo-Kemenes, T.
Institut für Physiologische Chemie, Physikalische
Biochemie und Zellbiologie
Universität München
Schillerstr. 44
D-8000 München 2
Federal Republic of Germany
(Chapter 16)

James, T.C.
Department of Molecular Biology and Biochemistry
Wesleyan University
Middletown, Connecticut 06457
USA
(Chapter 9)

Jantzen, K.
Institut für Physiologische Chemie, Physikalische
Biochemie und Zellbiologie
Universität München
Schillerstr. 44
D-8000 München 2
Federal Republic of Germany
(Chapter 16)

Kahl, G.
Fachbereich Biologie
Molekulare Pflanzenbiologie
Universität Frankfurt/Main
D-6000 Frankfurt/Main
Federal Republic of Germany
(Chapters 3 and 15)

Kaufman, L.S.
Department of Biological Sciences
University of Illinois
Chicago, Illinois 60680
USA
(Chapter 19)

Knebel, D.
Institut für Genetik
Universität Köln
D-5000 Köln
Federal Republic of Germany
(Chapter 21)

Kornberg, R.D.
Department of Cell Biology
Stanford University
School of Medicine
Stanford, California 94305
USA
(Chapter 11)

Langner, K.-D.
Institut für Genetik
Universität Köln
D-5000 Köln
Federal Republic of Germany
(Chapter 21)

LaPointe, J.W.
Department of Cell Biology
Stanford University School of Medicine
Stanford, California 94305
USA
(Chapter 11)

Lichtenberg, U.
Institut für Genetik
Universität Köln
D-5000 Köln
Federal Republic of Germany
(Chapter 21)

Linxweiler, W.
Institut für Physiologische Chemie, Physikalische Biochemie und Zellbiologie
Universität München
Goethestr. 33
D-8000 München 2
Federal Republic of Germany
(Chapter 12)

Lorch, Y.
Department of Cell Biology
Stanford University School of Medicine
Stanford, California 94305
USA
(Chapter 11)

Mathog, D.
Centro de Biologia Molecular del CSIC
Universidad Autonoma de Madrid
Cantoblanco, 28049 Madrid
Spain
(Chapter 26)

Meese, K.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 1)

Messing, J.
Waksman Institute, Rutgers
The State University of New Jersey
Piscataway, New Jersey 08854-0759
USA
(Chapter 2)

Müller, A.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 17)

Müller, U.
Institut für Genetik
Universität Köln
D-5000 Köln
Federal Republic of Germany
(Chapter 21)

Neubauer, B.
Institut für Physiologische Chemie, Physikalische Biochemie und Zellbiologie
Universität München
Goethestr. 33
D-8000 München 2
Federal Republic of Germany
(Chapter 12)

Neuer-Nitsche, B.
Institut für Zell- und Tumorbiologie
Abteilung Biochemie der Zelle
Deutsches Krebsforschungszentrum
Im Neuenheimer Feld 280
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 24)

Nordheim, A.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 1)

Nowock, J.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 16)

Paul, A.-L.
Laboratory of Plant Cell and Molecular Biology
University of Florida
Gainesville, Florida 32611
USA
(Chapter 20)

Pfeifer, G.P.
Zentrum für Biologische Chemie
Universität Frankfurt
D-6000 Frankfurt/Main
Federal Republic of Germany
(Chapter 23)

Püschel, A.W.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 17)

Renz, D.
Institut für Genetik
Universität Köln
D-5000 Köln
Federal Republic of Germany
(Chapter 21)

Rest, R.
Institut für Zell- und Tumorbiologie
Abteilung Biochemie der Zelle
Deutsches Krebsforschungszentrum
Im Neuenheimer Feld 280
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 24)

Runkel, L.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 1)

Rupp, R.A.W.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 17)

Saumweber, H.
Institut für Entwicklungsphysiologie
Universität Köln
Gyrhofstr. 171
D-5000 Köln
Federal Republic of Germany
(Chapter 26)

Schäfer, W.
Department of Plant Pathology
Cornell University
Ithaca, New York 14853-5908
USA
(Chapter 15)

Schell, J.
Max-Planck-Institut für Züchtungsforschung
Am Egelspfad
D-5000 Köln 30
Federal Republic of Germany
(Chapter 3)

Schiebel, K.
Institut für Biologie II
Lehrstuhl Genetik
Universität Tübingen
Auf der Morgenstelle 28
D-7400 Tübingen
Federal Republic of Germany
(Chapter 18)

Schlokat, U.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 4)

Schöler, H.R.
Boehringer Mannheim
Forschungszentrum (B-BRM2)
Bahnhofstr. 9-15
D-8132 Tutzing
Federal Republic of Germany
(Chapter 4)

Scholten, P.M.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 1)

Schröter, H.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 1)

Sedat, J.W.
Department of Biochemistry and Biophysics
University of California
San Francisco, California 94143
USA
(Chapter 26)

Shaw, P.E.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 1)

Sippel, A.E.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapters 16 and 17)

Smith, C.L.
Department of Genetics and Development
College of Physicians and Surgeons
Columbia University
New York, New York 10032
USA
(Chapter 27)

Spiker, S.
Genetics Department
North Carolina State University
Raleigh, North Carolina 27695-7614
USA
(Chapter 6)

Stief, A.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 17)

Strech-Jurk, U.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapters 17 and 17)

Theisen, M.
Zentrum für Molekulare Biologie
Universität Heidelberg
Im Neuenheimer Feld 282
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapters 16 and 17)

Thoma, F.
Institut für Zellbiologie
Eidgenössische-Technische-Hochschule-
Hönggerberg
8093 Zürich
Schweiz
(Chapters 7 and 13)

Thompson, W.F.
Department of Botany and Genetics
North Carolina State University
Raleigh, North Carolina 27695
USA
(Chapter 19)

Torres, R.A.
Institut für Biologie II
Lehrstuhl Genetik
Universität Tübingen
Auf der Morgenstelle 28
D-7400 Tübingen
Federal Republic of Germany
(Chapter 18)

Watson, J.C.
Department of Botany
University of Maryland
College Park, Maryland 20742
USA
(Chapter 19)

Weising, K.
Fachbereich Biologie
Molekulare Pflanzenbiologie
Universität Frankfurt/Main
D-6000 Frankfurt/Main
Federal Republic of Germany
(Chapters 3 and 15)

Weisshaar, B.
Institut für Genetik
Universität Köln
D-5000 Köln
Federal Republic of Germany
(Chapter 21)

Werner, D.
Institut für Zell- und Tumorbiologie
Abteilung Biochemie der Zelle
Deutsches Krebsforschungszentrum
Im Neuenheimer Feld 280
D-6900 Heidelberg 1
Federal Republic of Germany
(Chapter 24)

Yu, M.T.
Department of Genetics and Development
College of Physicians and Surgeons
Columbia University
New York, New York 10032
USA
(Chapter 27)

Zhang, X.Y.
Institut für Physiologische Chemie, Physikalische
Biochemie und Zellbiologie
Universität München
Goethestr. 33
D-8000 München 2
Federal Republic of Germany
(Chapter 12)

# Table of Contents

# I. DNA Structure and Gene Structure

# 1. Structural and Topological Polymorphism of DNA

*A. Nordheim, R.E. Herrera, K. Meese, L. Runkel, P.M. Scholten, H. Schröter and P.E. Shaw*

## 1.1 Introduction

After Watson and Crick (1953) formulated the concept of the complementary, double-helical nature of DNA, analyses of the structure and function of DNA rapidly shed light onto the molecular basis of biological processes. Much of our current understanding of molecular genetics is based on insights into the functions of DNA which themselves are determined to a large extent by the physical structure of the double-helix. In fulfilling its various biological activities under a variety of different intracellular conditions, DNA is able to undergo changes in conformation. Variability in DNA conformation forms the central focus of the present review. Whereas no detailed description of general aspects of DNA structure is intended, emphasis is placed on the aspect of flexibility of the double helix structure. The concept of DNA conformational polymorphism is dealt with at two levels. First, variations in DNA double helix structure *(structural DNA polymorphism)* are discussed regarding the three major double stranded DNA conformations (B-DNA, A-DNA, Z-DNA). Modulations of the B-DNA structure, as are found in complexes with proteins, are also described. Second, variations in helix geometry are considered with respect to the three-dimensional arrangement of DNA *(topological DNA polymorphism)*, i.e. conditions in which the direction of the helical axis deviates from the linear and, consequently, assumes distinct paths in space (DNA supercoiling, DNA curvature). Topological DNA polymorphism is defined in the context of this review as a description of variation in shape, appearance and spatial arrangement of double helical DNA in both topologically constrained DNA domains (linking number remains constant) and topologically unconstrained domains (linking number is not necessarily constant). Influences of protein binding on the three-dimensional folding of DNA (DNA bending, DNA looping) are included in this discussion. It is obvious that there is a relationship of mutual influence between double helix geometry and DNA three-dimensional topology.

## 1.2 Structural Polymorphism in the DNA Double-Helix

X-ray diffraction studies of synthetic DNA have allowed detailed analysis of double helix structure and its conformational variability. Structural polymorphism of DNA has been observed with DNA fibers (e.g.Les-

lie et al., 1980) as well as with single crystals of DNA (Wang et al,. 1979; Drew et al., 1981; Fig. 1-1). The high resolution, single-crystal X-ray analysis (made possible since the late 1970's due to advances in DNA oligonucleotide synthesis) has revealed fine details of DNA structure which have demonstrated the polymorphic nature of the DNA double helix. Crystal structures have been solved for the three major helical forms: A-DNA (Conner er al., 1982; Wang et al., 1982a; Shakked et al., 1983; McCall et al., 1985), B-DNA (Drew et al., 1981 and left-handed Z-DNA (Wang et al., 1979; Drew et al., 1980; see section 1.4). The distinguishing helical parameters of these three forms are given in Table 1-1 and are discussed in a number of detailed review articles (Zimmermann, 1982; Dickerson et al., 1982; Rich et al., 1984; Saenger, 1984; Shakked and Rabinovich, 1986; Jovin et al., 1987). Interestingly the finestructure of all three helical forms is influenced significantly by the primary nucleotide sequence (Drew et al., 1981; Dickersen and Drews, 1981; reviewed by Shakked and Rabinovich, 1986). Additional helix polymorphism has been observed in crystal analyses of DNA-drug complexes (Wang, 1987), DNA-RNA hybrids (Wang et al., 1982b), DNA mismatches (Kennard, 1987) and DNA segments containing Hoogsteen-type base pairing (Ughetto et al., 1985; Quigley et al., 1986).

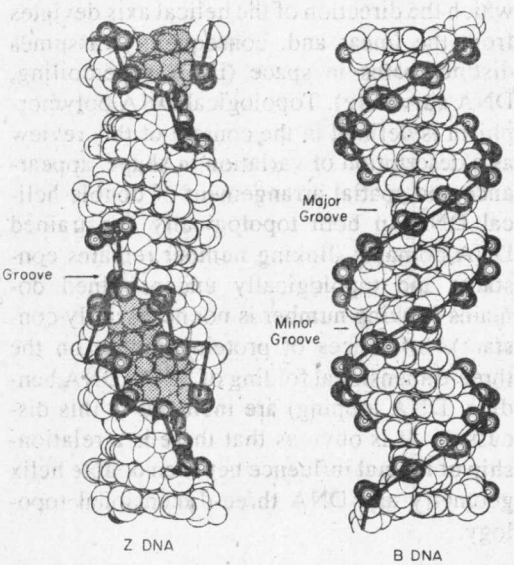


Fig. 1-1 Van der Waals drawings of right-handed B-DNA and left-handed Z-DNA (after Wang et al., 1979; with permission of A. Rich, MIT).

The observed helix polymorphism is associated with alterations in the different local helix parameters. These include tilt, twist, roll, propeller twist, base stacking interactions, slide geometry, sugar pucker and glycosyl bond rotation (syn/anti). DNA bending and intrinsic DNA curvature may contribute significantly to the spectrum of structural variation (see section 1.6). This spectrum is extended further by local discontinuities within a DNA segment. These include locally melted regions (Buc, 1987), DNA cruciforms (Lilley et al., 1987), junctions between two helix structures (e.g. B-Z or B-A junctions; Wang et al., 1979; Selsing et al., 1979), and sharp bends or kinks (Crick and Klug, 1975).

DNA polymorphism found in crystallographic studies of complexes between DNA and proteins is discussed separately in the next section (section 1.3). No detailed review, however, will be given here of the body of literature dealing with biochemical evidence for DNA structural polymorphism in solution (e.g. Depew and

Tab. 1-1 Global helical parameters for A-, B- and Z-DNA.

| DNA structure | crystallized oligonucleotide | Twist(°) | Rise (Å) | Bp/turn | Propeller twist | Reference |
|---|---|---|---|---|---|---|
| A-DNA | d(GGGGCCCC) | 31.6 | 2.9 | 11.4 | 10.3 | McCall et al., 1985 |
| B-DNA | d(CGCGAATTCGCG) | 37.3 | 3.3 | 9.7 | 13.0 | Drew et al., 1981 |
| Z-DNA | d(CGCGCG) | 60 (per dimer) | 7.6 (per dimer) | 12 | 4.6 | Wang et al., 1979 |