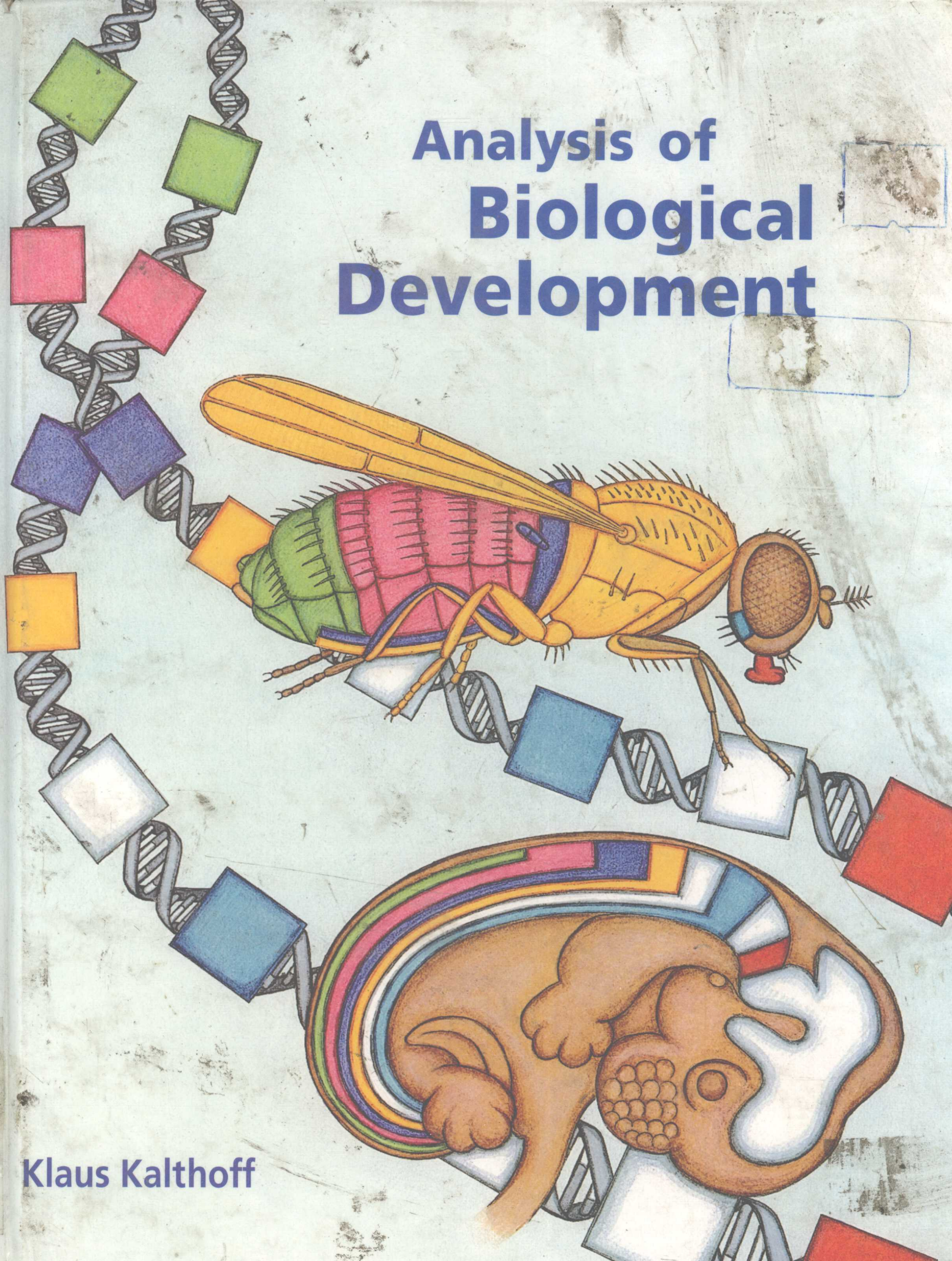
Analysis of Biological Development



Klaus Kalthoff

ANALYSIS OF BIOLOGICAL DEVELOPMENT

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Cover Illustration

Homeobox genes control development in animals as different as fruit flies and mice. These genes, represented here by colored boxes, occur in clusters on certain chromosomes; their hallmark is the homeobox, a stretch of DNA that has been conserved in evolution for more than 500 million years. Each homeobox gene is expressed in a certain domain within the epidermis of the fly and the central nervous system of the mouse. The location of a homeobox gene on a chromosome corresponds to where it is expressed in the body: the farther downstream it is located on the chromosome the more anterior it is expressed in the body. By regulating the activity of many other genes, homeobox genes control the morphological characteristics that develop in their expression domains. Thus, the antero-posterior body patterns of flies and mice are specified by nearly identical sets of regulatory genes.

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To My Teachers, Colleagues, and Students

ABOUT THE AUTHOR

Klaus Kalthoff is Professor of Zoology at The University of Texas at Austin. Born and raised in Germany, he studied biology at the universities of Erlangen, Hamburg, and Freiburg. He received his Ph.D. degree (Dr. rer. nat.) in 1971 from the University of Freiburg, where he completed his dissertation on pattern formation in insect embryos under the direction of Klaus Sander. Subsequent work done by Kalthoff and coworkers, also at Freiburg, showed that eggs of midges contain ribonucleoprotein particles acting as anterior determinants: they are localized near the anterior pole of the egg and are necessary for forming anterior body parts. Kalthoff also discovered that damage from ultraviolet light to certain insect eggs is reversible in a catalyzed reaction that depends on light of longer wavelength.

Kalthoff was awarded the Prize of the Scientific Society of Freiburg in 1975. He moved to Austin in 1978, where he and his coworkers characterized the RNA moiety of the anterior determinants in *Chironomus samoensis* as small, polyadenylated, and cytoplasmic. He is author or coauthor of numerous articles in scientific books and journals, including *Development, Developmental Biology, Nature, Photochemistry and Photobiology,* and *Proceedings of the National Academy of Sciences of the U.S.A.* Kalthoff teaches courses in developmental biology and human biology.

Developmental biology is both a classical and a modern field. Beginning with Wilhelm Roux and Hans Driesch late in the nineteenth century, a new generation of biologists ventured into the causal analysis of development. With hand-made glass needles and hair loops, they removed and transplanted parts of frog and sea urchin embryos to see what the parts would do in isolation and how they would interact with cells that were not their normal neighbors. By defining a new set of terms based on operational criteria, these scientists established experimental embryology as a new discipline. In 1924, Hans Spemann and Hilde Mangold published their famous "organizer" experiment, which showed that a transplanted piece of dorsal blastopore lip could induce surrounding host tissue to form a secondary embryo. This powerful demonstration epitomizes the first golden age of developmental biology.

Developmental biologists with a bent toward genetics soon found an alternative way of analyzing development. Studying mutant strains of various creatures, they began to uncover the logic of the genetic networks that control development. Those working with the fruit fly *Drosophila* learned that mutations in certain genes had dramatic effects on the overall body pattern, such as the replacement of certain body parts with parts that are normally formed elsewhere. This type of analysis was made more powerful by the introduction of mutagenesis screens, which can identify virtually all genes involved in the control of a developmental process. In the 1980s, genetic analysis was boosted again by the arrival of DNA cloning; now, the proteins encoded by patterning genes could be characterized in molecular terms. The prospect of knowing not only the mutant phenotypes of these genes, but also the biochemical properties of their products, energized hundreds of researchers. Today, the development of the *Drosophila* embryo is almost completely understood in terms of a network of gene activities that unfolds in a spatial order. The spectacular success of this work is being emulated by researchers working with other organisms. Developmental biology has entered another golden age.

Living in this second golden age is exhilarating. New and important discoveries are made every week. Just keeping up with the ever-growing literature has become a major effort, and so an undergraduate course in developmental biology is now a challenge for students and instructors alike. On the one hand, the classical foundations of development need to be preserved. On the other hand, the current excitement in developmental biology comes from bringing new and powerful tools to bear on some of the long-standing problems in the field. My answer to the challenge is this textbook, which is written for advanced undergraduates and beginning graduate students. I hope it will help them and their teachers to appreciate the rich heritage left by the classical development biologists and to savor the power and elegance of the new work.

The organization of the book reflects the union of classical and modern ways of analysis in contemporary developmental biology. Part One emphasizes classical methods of analysis and covers the series of embryonic stages from gametogenesis to histogenesis. Interspersed are basic conceptual topics such as nuclear totipotency, cell determination, cytoplasmic localization, induction, and morphogenesis. Part Two introduces the genetic and molecular analysis of development, beginning with a chapter on the use of mutants, DNA cloning, and transgenic organisms. Subsequent chapters explain the concept of differential gene expression with the goal of understanding how the genomic information is used to build a three-dimensional organism that unfolds in time. A chapter on paragenetic information provides a counterpoint to the emphasis on genetic information. Part Three freely combines classical and modern types of analysis and should be the most enjoyable portion of the book. It illustrates how the application of new research tools has led to a better understanding of long-standing issues in development. This part features a set of chapters on pattern formation, one of the central topics in developmental biology. Cell differentiation, sex determination, hormonal control, growth, and the roles of cell adhesion and extra cellular materials in morphogenesis round out what should be a fair representation of contemporary developmental biology.

Facing a plethora of old and new results, I found it important to bring out about a dozen general principles. For instance, many steps in development rely on synergistic mechanisms that complement or reinforce each other. Spemann referred to this as the principle of double insurance; I introduce this principle in the context of fertilization and then take it up again in chapters on induction and genetic control. Other principles, including stepwise approximation and default programs, are treated in a similar fashion.

The textbook in developmental biology that I used as a student was Alfred Kühn's *Entwicklungsphysiologie.* I have adopted Kühn's habit of discussing key experiments in some detail. When introducing transgenic organisms, I describe the germ line transformation of *rosy* mutant fruit flies with the wild-type transgene. This description makes it necessary to explain the method of Southern blotting. Experiment descriptions are marked with colored bars, and explanations of methods are boxed. I hope that readers will find these sections especially worthwhile. Including experiment descriptions while keeping chapters to a manageable length has made it necessary to present materials selectively. In most chapters, one or two subtopics are discussed in more

depth than the others, and these subtopics are marked with color in the list of contents for the chapter.

On various occasions throughout the text, I point out problems whose solutions remain elusive. I hope this will convey the spirit of science as an endeavor in which answers bear new questions and in which one generation passes the torch on to the next.

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I feel grateful to some special people who provided inspiration and support for writing this text. My mentor, Klaus Sander, long ago introduced me to the history and culture of developmental biology. When I came to The University of Texas at Austin, I met a congenial group of colleagues including Gary Freeman, Antone Jacobson, Bill Jeffery, the late Stephen Meier, and Matt Winkler. In countless journal club sessions and lunch conversations, they broadened my outlook on developmental biology and its practitioners. My wife, Karin, and sons, Christian, Ulrich, and Philipp, gave me the freedom and peace of mind to spend long hours in front of journals and computers screens.

Carrying this text the long way from first draft to bound book has required the help of many people, to whom I express my appreciation. First and foremost, I thank Kathi Prancan, sponsoring editor at McGraw-Hill, for skillfully guiding this complex project to completion, and for going several extra miles in doing so. Judith Kromm read my first draft and nudged me from writing review articles to writing textbook chapters. Richard K. Mickey expertly copyedited the final manuscript. Janet Young supervised the artwork, and Linda McVay prepared the hand-drawn illustrations. Safra Nimrod, Mira Schachne, Ondine Cleaver, and Flora Love helped to assemble the photographs that speak better than words. Many colleagues were very diligent and courteous in providing their prints or negatives. Keithley and Associates designed the cover and text. Holly Gordon assembled all parts of the manuscript with great attention to detail. Lewis Patterson, Rachel Savage, Karen Nordby, Kelli Baxter, and Hemant Makan helped with proofreading, indexing, and clerical work and kept me going.

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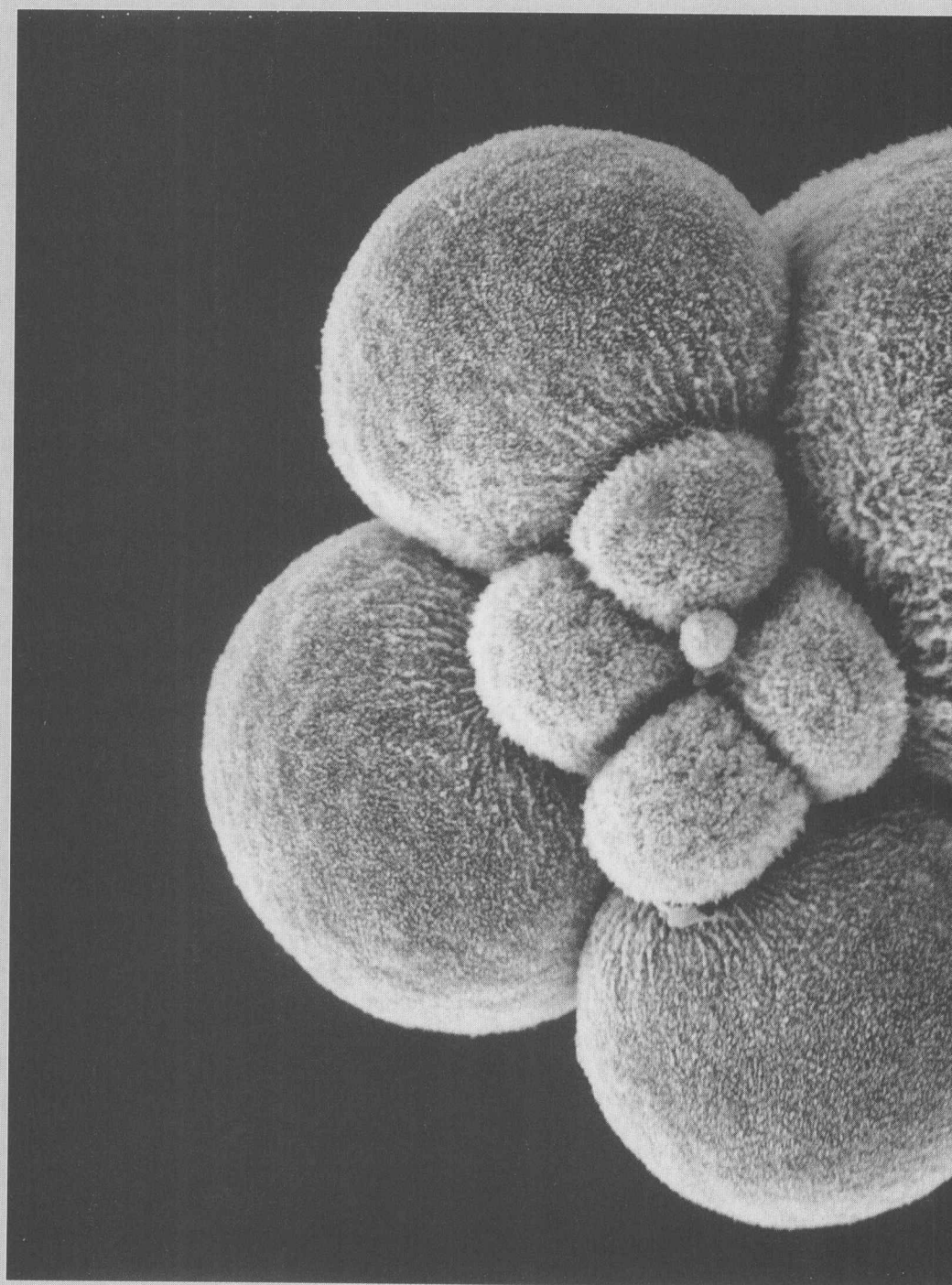

Figure I.1 Scanning electron micrograph of a snail embryo (*Ilyanassa obsoleta*) at the 8-cell stage. (The tiny cell at the center is a polar body.) The four smaller cells, or micromeres, are rotated clockwise relative to their larger sister cells, or macromeres. One macromere is larger than the other three macromeres because it has incorporated a special mass of cytoplasm. The asymmetrical localization of this cytoplasm endows the largest macromere and its descendants with specific developmental capabilities.

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