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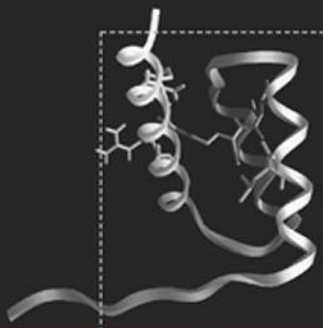

BIOINFORMATICS

A Practical Guide to the Analysis of Genes and Proteins

EDITED BY
ANDREAS D. BAXEVANIS
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METHODS OF
BIOCHEMICAL ANALYSIS

Volume 43

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A Practical Guide to the Analysis of Genes and Proteins

SECOND EDITION

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ADB dedicates this book to his Goddaughter, Anne Terzian, for her constant kindness, good humor, and love—and for always making me smile.

BFFO dedicates this book to his daughter, Maya. Her sheer joy and delight in the simplest of things lights up my world everyday.

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FOREWORD

I am writing these words on a watershed day in molecular biology. This morning, a paper was officially published in the journal *Nature* reporting an initial sequence and analysis of the human genome. One of the fruits of the Human Genome Project, the paper describes the broad landscape of the nearly 3 billion bases of the euchromatic portion of the human chromosomes.

In the most narrow sense, the paper was the product of a remarkable international collaboration involving six countries, twenty genome centers, and more than a thousand scientists (myself included) to produce the information and to make it available to the world freely and without restriction.

In a broader sense, though, the paper is the product of a century-long scientific program to understand genetic information. The program began with the rediscovery of Mendel's laws at the beginning of the 20th century, showing that information was somehow transmitted from generation to generation in discrete form. During the first quarter-century, biologists found that the cellular basis of the information was the chromosomes. During the second quarter-century, they discovered that the molecular basis of the information was DNA. During the third quarter-century, they unraveled the mechanisms by which cells read this information and developed the recombinant DNA tools by which scientists can do the same. During the last quarter-century, biologists have been trying voraciously to gather genetic information-first from genes, then entire genomes.

The result is that biology in the 21st century is being transformed from a purely laboratory-based science to an information science as well. The information includes comprehensive global views of DNA sequence, RNA expression, protein interactions or molecular conformations. Increasingly, biological studies begin with the study of huge databases to help formulate specific hypotheses or design large-scale experiments. In turn, laboratory work ends with the accumulation of massive collections of data that must be sifted. These changes represent a dramatic shift in the biological sciences.

One of the crucial steps in this transformation will be training a new generation of biologists who are both computational scientists and laboratory scientists. This major challenge requires both vision and hard work: vision to set an appropriate agenda for the computational biologist of the future and hard work to develop a curriculum and textbook.

James Watson changed the world with his co-discovery of the double-helical structure of DNA in 1953. But, he also helped train a new generation to inhabit that new world in the 1960s and beyond through his textbook, *The Molecular Biology of the Gene*. Discovery and teaching go hand-in-hand in changing the world.

In this book, Andy Baxevanis and Francis Ouellette have taken on the tremendously important challenge of training the 21st century computational biologist. Toward this end, they have undertaken the difficult task of organizing the knowledge in this field in a logical progression and presenting it in a digestible form. And, they have done an excellent job. This fine text will make a major impact on biological research and, in turn, on progress in biomedicine. We are all in their debt.

Eric S. Lander

February 15, 2001
Cambridge, Massachusetts

PREFACE

With the advent of the new millenium, the scientific community marked a significant milestone in the study of biology—the completion of the ''working draft'' of the human genome. This work, which was chronicled in special editions of *Nature* and *Science* in early 2001, signals a new beginning for modern biology, one in which the majority of biological and biomedical research would be conducted in a ''sequence-based'' fashion. This new approach, long-awaited and much-debated, promises to quickly lead to advances not only in the understanding of basic biological processes, but in the prevention, diagnosis, and treatment of many genetic and genomic disorders. While the fruits of sequencing the human genome may not be known or appreciated for another hundred years or more, the implications to the basic way in which science and medicine will be practiced in the future are staggering. The availability of this flood of raw information has had a significant effect on the field of bioinformatics as well, with a significant amount of effort being spent on how to effectively and efficiently warehouse and access these data, as well as on new methods aimed at mining this warehoused data in order to make novel biological discoveries.

This new edition of *Bioinformatics* attempts to keep up with the quick pace of change in this field, reinforcing concepts that have stood the test of time while making the reader aware of new approaches and algorithms that have emerged since the publication of the first edition. Based on our experience both as scientists and as teachers, we have tried to improve upon the first edition by introducing a number of new features in the current version. Five chapters have been added on topics that have emerged as being important enough in their own right to warrant distinct and separate discussion: expressed sequence tags, sequence assembly, comparative genomics, large-scale genome analysis, and BioPerl. We have also included problem sets at the end of most of the chapters with the hopes that the readers will work through these examples, thereby reinforcing their command of the concepts presented therein. The solutions to these problems are available through the book's Web site, at **www.wiley.com/bioinformatics**. We have been heartened by the large number of instructors who have adopted the first edition as their book of choice, and hope that these new features will continue to make the book useful both in the classroom and at the bench.

There are many individuals we both thank, without whose efforts this volume would not have become a reality. First and foremost, our thanks go to all of the authors whose individual contributions make up this book. The expertise and professional viewpoints that these individuals bring to bear go a long way in making this book's contents as strong as it is. That, coupled with their general good-

naturedness under tight time constraints, has made working with these men and women an absolute pleasure.

Since the databases and tools discussed in this book are unique in that they are freely shared amongst fellow academics, we would be remiss if we did not thank all of the people who, on a daily basis, devote their efforts to curating and maintaining the public databases, as well as those who have developed the now-indispensible tools for mining the data contained in those databases. As we pointed out in the preface to the first edition, the bioinformatics community is truly unique in that the *esprit de corps* characterizing this group is one of openness, and this underlying philosophy is one that has enabled the field of bioinformatics to make the substantial strides that it has in such a short period of time.

We also thank our editor, Luna Han, for her steadfast patience and support throughout the entire process of making this new edition a reality. Through our extended discussions both on the phone and in person, and in going from deadline to deadline, we've developed a wonderful relationship with Luna, and look forward to working with her again on related projects in the future. We also would like to thank Camille Carter and Danielle Lacourciere at Wiley for making the entire copy-editing process a quick and (relatively) painless one, as well as Eloise Nelson for all of her hard work in making sure all of the loose ends came together on schedule.

BFFO would like to acknowledge the continued support of Nancy Ryder. Nancy is not only a friend, spouse, and mother to our daughter Maya, but a continuous source of inspiration to do better, and to challenge; this is something that I try to do every day, and her love and support enables this. BFFO also wants to acknowledge the continued friendship and support from ADB throughout both of these editions. It has been an honor and a privilege to be a co-editor with him. Little did we know seven years ago, in the *second* basement of the Lister Hill Building at NIH where we shared an office, that so many words would be shared between our respective computers.

ADB would also like to specifically thank Debbie Wilson for all of her help throughout the editing process, whose help and moral support went a long way in making sure that this project got done the right way the first time around. I would also like to extend special thanks to Jeff Trent, who I have had the pleasure of working with for the past several years and with whom I've developed a special bond, both professionally and personally. Jeff has enthusiastically provided me the latitude to work on projects like these and has been a wonderful colleague and friend, and I look forward to our continued associations in the future.

Andreas D. Baxevanis
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