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Next-Generation Genome Sequencing

Towards Personalized Medicine

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Preface

The development of the rapid DNA sequencing method by Fred Sanger and co-workers 30 years ago initiated the process of deciphering genes and eventually entire genomes. The rapidly growing demand for throughput, with the ultimate goal of deciphering the human genome, led to substantial improvements in the technique and was exemplified in automated capillary electrophoresis. Until recently, genome sequencing was performed in large sequencing centers with high automation and many personnel. Even when DNA sequencing reached the industrial scale, it still cost $10 million and 10 years to generate a draft of the human genome. With the price so high, population-based phenotype–genotype linkage studies were small in scale, and it was hard to translate research into statistically robust conclusions. As a consequence, most presumed associations between diseases and particular genes have not stood up to scientific scrutiny. The commercialization of the first massive parallel pyrosequencing technique in 2004 created the first opportunity for the cost-effective and rapid deciphering of virtually any genome. Shortly thereafter, other vendors entered the market, bringing with them a vision of sequencing the human genome for only $1000.

This is the topic of this book. We hope to provide the reader with a comprehensive overview of next-generation sequencing (NGS) techniques and highlight their impact on genome research, human health, and the social perception of genetics.

There is no clear definition of next-generation sequencing. There are, however, several features that distinguish NGS platforms from conventional capillary-based sequencing. First, it has the ability to generate millions of sequence reads rather than only 96 at a time. This process allows the sequencing of an entire bacterial genome within hours or of the *Drosophila melanogaster* genome within days instead of months. Furthermore, conventional vector-based cloning, typical in capillary sequencing, became obsolete and was replaced by direct subjecting of fragmented, and usually, amplified DNA for sequencing. Another distinctive feature of NGS are the sequenced products themselves, which are short-length reads between 30 and 400 bp. The limited read length has substantial impact on certain NGS applications, for instance, *de novo* sequencing. The following chapters will present several innovative approaches, which will combine the obvious advantages of NGS, such as

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throughput and simplified template preparation, with novel challenging features in terms of short read assembly and large sequencing data storage and processing.

This book arose from the recognition of the need to understand next-generation sequencing techniques and their role in future genome research by the broad scientific community. The chapters have been written by the researchers and inventors who participated in the development and applications of NGS technologies. The first chapter of the book contains an excellent overview on Sanger DNA sequencing, which still remains the gold standard in life sciences. The second and fourth parts of the book describe the commercially available and emerging sequencing platforms, respectively. The third part consists of two chapters highlighting the bottlenecks in the current sequencing: data storage and processing. Once the NGS techniques became available, an unprecedented explosion of applications could be observed. The fifth part of this book provides the reader with the insight into the ever-increasing NGS applications in genome research. Some of these applications are enhancements of existing techniques. Many others are unique to next-generation sequencing marked by its robustness and cost effectiveness, with the prominent example of paleogenomics.

The versatility and robustness of the NGS techniques in studying genes in the context of the entire genome surprised many scientists, including myself. We know that the processes that cause most diseases are not the result of a single genetic failure. Instead, they involve the interaction of hundreds if not thousands of genes. In the past, geneticists have concentrated on genes that have large individual effects when they go wrong, because those effects are so easy to spot. However, combinations of genes that are not individually significant may also be important. It has become evident that next-generation sequencing techniques, together with systems biology approaches, could elucidate the complex dependences of regulatory networks not only on the level of a single cell or tissue but also on the level of the whole organism.

We hope that this book will enrich the understanding of the dramatic changes in genome exploration and its impact not only on research itself but also on many aspects of our life, including healthcare policy, medical diagnostics, and treatment. The best example comes from the field of consumer genomics. Consumer genomics promises to inform people of their risks of developing ailments such as heart disease or cancer; it can even advise its customers how much coffee they can safely drink. This information is retrieved from the correlation of the single nucleotide polymorphism (SNP) pattern of the individual with the SNP haplotype linked to a particular disease. Recent public discussions on the challenges posed by the availability of personal genome information have revealed a new perception of genomic information and its uses. For the first time, a desire to understand the genome has become important and relevant to people outside of the scientific community. In addition to the benefits of having access to genetic information, the ethical and legal risks of making this information available are emerging. The last part of the book introduces the reader to the debate, which will only intensify in the years to come.

In conclusion, I would like to express my sincere gratitude to all of the contributors for their extraordinary effort to present these fascinating technologies and their applications in genome exploration in such a clear and comprehensive way. I also extend my thanks to Professor Hans Lehrach for his constant support.

Berlin, July 2008 *Michal Janitz*

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