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Introduces readers to core algorithmic techniques for next-generation sequencing (NGS) data analysis and discusses a wide range of computational techniques and applications This book provides an in-depth survey of some of the recent developments in NGS and discusses mathematical and computational challenges in various application areas of NGS technologies.

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Next generation sequencing (NGS) has made great strides in sequencing technology as it enables sequencing of genes in a high throughput manner with low cost. Various NGS platforms such as Illumina, Roche, ABI/SOLiD are used for wet-lab analysis of NGS data and computational tools such as BWA, Bowtie, Galaxy, SanGeniX are used for dry-lab analysis of NGS data.

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In summary, computational prediction methods are essential for the implementation of NGS into clinical decision-making. While much progress has been made and a plethora of conceptually diverse tools is already available, there is a need to develop specialized methods that are optimized for the prediction of variant functionality rather than pathogenicity and are calibrated specifically on pharmacogenetic data.

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Second, our lack of a systematic comparison of error-correction methods impedes the optimal integration of these tools into standardized next-generation sequencing data analysis pipelines. Fig. 1 Study design for benchmarking computational error-correction methods.

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Introduces readers to core algorithmic techniques for next-generation sequencing (NGS) data analysis and discusses a wide range of computational techniques and applications This book provides an in-depth survey of some of the recent developments in NGS and discusses mathematical and computational challenges in various application areas of NGS technologies. The 18 chapters featured in this book have been authored by bioinformatics experts and represent the latest work in leading labs actively contributing to the fast-growing field of NGS. The book is divided into four parts: Part I focuses on computing and experimental infrastructure for NGS analysis, including chapters on cloud computing, modular pipelines for metabolic pathway reconstruction, pooling strategies for massive viral sequencing, and high-fidelity sequencing protocols. Part II concentrates on analysis of DNA sequencing data, covering the classic scaffolding problem, detection of genomic variants, including insertions and deletions, and analysis of DNA methylation sequencing data. Part III is devoted to analysis of RNA-seq data. This part discusses algorithms and compares software tools for transcriptome assembly along with methods for detection of alternative splicing and tools for transcriptome quantification and differential expression analysis. Part IV explores computational tools for NGS applications in microbiomics, including a discussion on error correction of NGS reads from viral populations, methods for viral quasispecies reconstruction, and a survey of state-of-the-art methods and future trends in microbiome analysis. Computational Methods for Next Generation Sequencing Data Analysis: Reviews computational techniques such as new combinatorial optimization methods, data structures, high performance computing, machine learning, and inference algorithms Discusses the mathematical and computational challenges in NGS technologies Covers NGS error correction, de novo genome transcriptome assembly, variant detection from NGS reads, and more This text is a reference for biomedical professionals interested in expanding their knowledge of computational techniques for NGS data analysis. The book is also useful for graduate and post-graduate students in bioinformatics.

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Recently, next generation sequencing (NGS) technology has emerged as a powerful approach and dramatically transformed biomedical research in an unprecedented scale. NGS is expected to replace the traditional hybridization-based microarray technology because of its affordable cost and high digital resolution. Although NGS has significantly extended the ability to study the human genome and to better understand the biology of genomes, the new technology has required profound changes to the data analysis. There is a substantial need for computational methods that allow a convenient analysis of these overwhelmingly high-throughput data sets and address an increasing number of compelling biological questions which are now approachable by NGS technology. This dissertation focuses on the development of computational methods for NGS data analyses. First, two methods are developed and implemented for detecting variants in analysis of individual or pooled DNA sequencing data. SNVer formulates variant calling as a hypothesis testing problem and employs a binomial-binomial model to test the significance of observed allele frequency by taking account of sequencing error. SNVerGUI is a GUI-based desktop tool that is built upon the SNVer model to facilitate the main users of NGS data, such as biologists, geneticists and clinicians who often lack of the programming expertise. Second, collapsing singletons strategy is explored for associating rare variants in a DNA sequencing study. Specifically, a gene-based genome-wide scan based on singleton collapsing is performed to analyze a whole genome sequencing data set, suggesting that collapsing singletons may boost signals for association studies of rare variants in sequencing study. Third, two approaches are proposed to address the 3'UTR switching problem. PolyASeeker is a novel bioinformatics pipeline for identifying polyadenylation cleavage sites from RNA sequencing data, which helps to enhance the knowledge of alternative polyadenylation mechanisms and their roles in gene regulation. A change-point model based on a likelihood ratio test is also proposed to solve such problem in analysis of RNA sequencing data. To date, this is the first method for detecting 3'UTR switching without relying on any prior knowledge of polyadenylation cleavage sites.

Large-scale changes are taking place in the way modelling is performed within the US EPA, and a new generation of environmental models is currently under construction. The US EPA is engaging in several modelling efforts in response to Congressional mandates such as the Clean Air Act and the Clean Water Act. These mandates require the scientific modelling of the impact of pollutants on human health and the environment. The complexity of scale in environmental models has increased by several orders of magnitude, with a simultaneous demand for increased stability, accuracy and efficiency in the computed model solution. This book showcases numerical algorithms appropriate to the subject areas listed below and explores how new algorithmic methods would benefit the US EPA's environmental models and other environmental studies.

In this study we build solutions to three common challenges in the fields of bioinformatics through utilizing statistical methods and developing computational approaches. First, we address a common problem in genome wide association studies, which is linking genotype features within organisms of the same species to their phenotype characteristics. We specifically studied FHA domain genes in Arabidopsis thaliana distributed within Eurasian regions by clustering those plants that share similar genotype characteristics and comparing that to the regions from which they were taken. Second, we also developed a tool for calculating transposable element density within different regions of a genome. The tool is built to utilize the information provided by other transposable element annotation tools and to provide the user with a number of options for calculating the density for various genomic elements such as genes, piRNA and miRNA or for the whole genome. It also provides a detailed calculation of densities for each family and sub-family of the transposable elements. Finally, we address the problem of mapping multi reads in the genome and their effects on gene expression. To accomplish this, we implemented methods to determine the statistical significance of expression values within the genes utilizing both a unique and multi-read weighting scheme. We believe this approach provides a much more accurate measure of gene expression than existing methods such as discarding multi reads completely or assigning them randomly to a set of best assignments, while also providing a better estimation of the proper mapping locations of ambiguous reads. Overall, the solutions we built in these studies provide researchers with tools and approaches that aid in solving some of the common challenges that arise in the analysis of high throughput sequence data.

Historically, much of the research in evolutionary biology and population genetics has involved analysis at the level of either a single locus or a few number thereof. However, Next Generation sequencing technology has opened the floodgates with respect to both the sheer volume and quality of sequence data that researchers have long needed to address and answer long-standing questions in their fields. Scientists are now, by and large, no longer hampered in their efforts by technological hurdles to obtain data, but are in fact facing the problem of how best to use the vast amount of data that are accumulating at an ever-increasing rate. This is a good problem to have. The following research described in this dissertation is an attempt to derive answers to questions in the fields of population genetics and evolutionary biology that, until recently, have been either intractable or, at best, extremely difficult to address. In the first chapter I provide an introduction and a brief historical look at the research efforts that have proceeded my own. In the second chapter I describe how modern sequencing methods and computational analysis can be used to study, analyze, and answer evolutionary questions about the non-model organism, Enallagma hageni, in order to 1) determine this organism's phylogenetic position within Arthropoda, 2) provide answers and insight into the evolutionary history of the protein-encoding genes in the Enallagma transcriptome, and 3) give functional annotation to these expressed proteins. In the third chapter I examine how natural selection acts on the genome and derive a method that can accurately determine the evolutionary cause of nucleotide fixations, having occurred either through positive selection or neutral processes. I then apply the methodology to North American populations of Drosophila melanogaster, providing further evidence as to how adaptive evolution proceeds in a newly established population. This is an important question, for though there have been multiple approaches devised to determine the targets and modes of evolution in the genome, to date there has not emerged a definitive method which can determine both the location and type of a selective process, and as a result, the picture of how and where adaptive evolution proceeds in the genome has remained opaque. In the forth chapter I examine how levels of natural selection within the genome have the potential to inhibit the ability to accurately learn population demographic history. Using a number of modern algorithms and extensive simulations, I first examine whether or not demographic histories that are learned under simple biological assumptions will yield accurate results when the actual data itself does not adhere to these assumptions. Further, I go on to examine more complicated models of demographic history, looking specifically at how positive selection biases inference, which directions these biases occur, and at what levels of selection do inference methods fail to be robust. Finally, I describe potential evolutionary scenarios where these inference methods may be more prone to fail, as well as methods which might mitigate positive selection's effects, thus allowing for more accurate histories to be inferred. The work contained in this dissertation, at the broadest scale, is an effort to marry state-of-the-art techniques in statistics, computer science, and machine learning algorithms to the technological advances of next generation sequencing; the potent combination of these technologies has provided a means with which to derive answers to multiple, long-standing questions in population genetics and evolutionary biology.

The recent rapid innovations in supercomputer technology are changing the concepts of numerical calculations employed in solving a wide variety of nuclear many-body problems. The purpose of the XVII RCNP International Symposium on Innovative Computational Methods in Nuclear Many-Body Problems (INNOCOM97) was to discuss the frontiers of various computational methods and to exchange ideas in wide fields of nuclear physics. The subjects discussed at the symposium covered almost all the areas of nuclear physics.