

# Introduction to Bioinformatics and Computational Biology

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# Chapter 1

## Course information

This is the course material for STAT115/215 BIO/BST282 at Harvard University.

### 1.1 Contributors

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## Chapter 2

# Introduction

### 2.1 Welcome

### 2.2 Brief history of bioinformatics

#### 2.2.1 Protein structure wave

#### 2.2.2 Gene expression wave

#### 2.2.3 Genome sequencing wave

#### 2.2.4 High throughput sequencing

#### 2.2.5 Big data challenge from sequencing

### 2.3 Should I take this course?

#### 2.3.1 Bioinformatics vs computational biology

#### 2.3.2 Levels of bioinformatics

#### 2.3.3 Is this class for me?

#### 2.3.4 All biology is computational biology

### 2.4 Course information

#### 2.4.1 Course organization and material

#### 2.4.2 Course instructor and TAs

#### 2.4.3 Homework and grading

#### 2.4.4 Lab and Odyssey sign up

## Chapter 3

# High throughput sequencing

### 3.1 Three generations of sequencing technologies

First generation sequencing is Sanger sequencing. It is the technology that was used to obtain the first human genome sequence.

Second generation sequencing is also called next generation sequencing (NGS) and is the start of high throughput sequencing. It is what scientists use most often nowadays, and Illumina is the market leader. Most of the rest of this course will cover data analysis using second generation sequencing.

Third generation sequencing is single-molecule sequencing. There are many new technologies still under active development, although none has reached market penetration.

### 3.2 FASTQ and FASTQC

NGS generates FASTQ files. FASTQC is an computational approach to evaluate the quality of your NGS data.

### 3.3 Early sequence alignment (1 with 1)

In the early days (1970s), scientists were not worried about having to align too many sequences. They wanted to find the best alignment between two

sequences. Many bioinformatics courses start with learning these, although it is not the main focus of our course. We included two videos in case you are interested.

The Needleman-Wunsch algorithm is the earliest algorithm to find the alignment between two sequences and score their similarity.

When two sequences are long, and only a portion of them can align well with each other, the Smith-Waterman algorithm can find the best local sequence alignment. It is still considered the best alignment approach, although it is slow.

### 3.4 Sequence search algorithms (1 with many)

With more and more sequences available in the public in the 1980s, scientists were interested in finding whether their newly sequenced string has been sequenced before in the public database. Therefore, the fast search algorithm BLAST was developed, using one sequence as the query to find similar sequences from a database.

### 3.5 Borrow-Wheeler Aligner (many with many)

With NGS, scientists need much faster search (aka mapping) algorithms in order to align the millions of sequences to the reference genome. The current best algorithm is called Borrow-Wheeler Aligner or BWA.

In order to understand BWA, we first need to introduce Borrow-Wheeler transformation and LF mapping

The basic idea of Borrow-Wheeler alignment

### 3.6 Alignment output

NGS raw data is in FASTQ. Alignment gives you SAM (alignment) or BAM (binary version of SAM) files which contain the sequence information in FASTQ and the mapping locations. BED file is the simplest, although there is information loss.



## Chapter 4

# RNA-seq quantification

4.1 RNA-seq & RNA QC (DV200)

4.2 RNA-seq replicates and study design

4.3 STAR and PE BAM file

4.4 RNA-seq QC

4.5 FPKM vs TPM

4.6 RSEM & Salmon



## Chapter 5

# Differential expression, False discovery rate, Gene ontology

### 5.1 RNA-seq NB distribution

### 5.2 DESeq2 and variance stabilization

### 5.3 Multiple hypotheses testing and FWER

### 5.4 FDR

### 5.5 GO



## Chapter 6

# GSEA, Clustering

### 6.1 GSEA

### 6.2 Heatmap and clustering quality

### 6.3 H-cluster

### 6.4 K-means

### 6.5 Pick K and consensus clustering

### 6.6 Batch effect removal



## Chapter 7

# Dimension Reduction

### 7.1 MDS

### 7.2 LDA

### 7.3 PCA





## Chapter 8

# Classification

8.1 Intro to machine learning

8.2 Cross validation

8.3 Regression

8.4 Regularization

8.5 KNN

8.6 Decision trees

8.7 Random forest

8.8 SVM



## Chapter 9

# Module I Review

### 9.1 Gene Expression Module Summary

### 9.2 Gene Expression Analysis Scenarios



## Chapter 10

# Transcription Factor Motif Finding

10.1 Transcription regulation

10.2 Motif representation

10.3 EM

10.4 Gibbs sampler

10.5 Gibbs intuition

10.6 Motif finding in eukaryotes

10.7 Known motif database



## Chapter 11

# ChIP-seq, Expression Integration

11.1 ChIP-seq

11.2 BWA and MACS

11.3 ChIP-seq QC

11.4 TF interactions (motif)

11.5 TF target genes (expression integration)





## Chapter 12

# Epigenetics, DNA Methylation

12.1 Epigenetics

12.2 DNA methylation

12.3 Promoter function

12.4 Gene body function

12.5 Enhancer function

12.6 Repetitive region function

12.7 Early cancer detection



## Chapter 13

# Histone Modifications , Chromatin Accessibility

13.1 Nucleosome positions

13.2 Histone modification

13.3 Promoters (bivalent)

13.4 Genes (K36me3, new genes)

13.5 Enhancers (K27ac)

13.6 Super-enhancers

13.7 DNase-seq

13.8 ATAC-seq



## Chapter 14

# Long Range Chromatin Interactions

14.1 Chromatin interactions

14.2 HiC

14.3 HiC contact map

14.4 HiC normalization

14.5 Fractal globule

14.6 Loops

14.7 Domains

14.8 Compartments

14.9 Phase separation



## Chapter 15

# Hidden Markov Model

15.1 Intro to HMM

15.2 Pb1: Forward & backward procedure

15.3 Pb2: Viterbi algorithm

15.4 Pb3: Parameter estimation

15.5 HMM application





## Chapter 16

# Module II Review

### 16.1 Module II Review

### 16.2 Practive Questions



## Chapter 17

# SNP and GWAS

### 17.1 SNP and LD

### 17.2 Family-based vs case-control association studies

### 17.3 GWAS studies and catalog

### 17.4 GTEx and eQTL



## Chapter 18

# GWAS and Epigenomics

18.1 Find tissue / cell type

18.2 Identify causal SNPs and genes

18.3 Predict phenotypes



## Chapter 19

# Single-cell RNA-seq (1)

19.1 Intro to scRNA-seq

19.2 Smart, Droplet, microwell, SCI-based

19.3 QC

19.4 Normalization

19.5 Imputation

19.6 Dimension reduction

19.7 Clustering

19.8 t-SNE and UMAP





## Chapter 20

# Single-cell RNA-seq (2)

20.1 Annotate scRNA-seq clusters

20.2 Differential expression

20.3 Batch effect removal

20.4 Pseudotime

20.5 Overload 10X

20.6 Other applications (CITE-seq, multi-seq, spatial transcriptomics)



## Chapter 21

# scATAC-seq

21.1 Intro to scATAC-seq

21.2 Sample and cell QC

21.3 Dimension reduction, clustering & visualization

21.4 Differential peaks and annotations

21.5 Integration with scRNA-seq



## Chapter 22

# Module III Review

### 22.1 Module III Review



## Chapter 23

# Cancer Genome Sequencing , Mutation analyses

23.1 Intro to TCGA

23.2 Cancer mutation characterization

23.3 Cancer mutation patterns

23.4 Tumor purity and clonality

23.5 Interpret tumor mutations

23.6 Find cancer genes

23.7 Summary and future





## Chapter 24

# Cancer Subtyping, Survival Analyses

24.1 TCGA expression

24.2 Tumor subtypes

24.3 Survival analysis

24.4 GoF Oncogenes and LoF TS

24.5 Chromatin regulator mutations in cancer

24.6 DNA methylation and CIMP





## Chapter 25

# Targeted Therapy, Drug Resistance, Compound and Genetic Screens

25.1 Hallmarks of cancer

25.2 Chemo vs targeted therapy

25.3 Drug resistance

25.4 Synthetic lethality

25.5 Precision medicine

25.6 Tumor (bulk vs scRNA-seq), mice, cell lines

25.7 Compound screens

25.8 Genetic screens

25.9 Tumor heterogeneity

## Chapter 26

# Cancer Immunotherapy (1)

26.1 Systemic immunotherapy

26.2 Personalized immunotherapy

26.3 HLA and neoantigens

26.4 Tumor immune deconvolution

26.5 T cell signaling (PD1/PDL1, etc)

26.6 Other immune-cells (scRNA-seq)



## Chapter 27

# Cancer Immunotherapy (2)

27.1 TCR analysis

27.2 BCR analysis

27.3 Microbiome

27.4 Immunotherapy response biomarkers

27.5 Targeted therapy as immune-modulators

27.6 Epigenetic therapy as immune-modulators





## Chapter 28

# CRISPR Screens

28.1 CRISPR and KO

28.2 CRISPRa and CRISPRi

28.3 CRISPR design and outcome

28.4 CRISPR screens & DepMap

28.5 CRISPR screen analysis

28.6 CRISPR screens in drug response

28.7 CRISPR screens in immunology

28.8 Enhancer CRISPR screen

28.9 CRISPR screens + scRNA-seq



## **Chapter 29**

# **Module IV Review and Course Review**

### **29.1 Module IV Review**

### **29.2 Course Review**