

# 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.

All the YouTube videos in this course are organized under the 2021 STAT115 playlist.

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We thank many colleagues in the community, who helped Dr. Liu in prepare the STAT115/215 BIO/BST282 course over the years. Some of the lecture slides acknowledged their contributions, but these contributors are not individually acknowledged here.



## Chapter 2

# Introduction

### 2.1 Brief history of bioinformatics

#### 2.1.1 Protein structure wave

#### 2.1.2 Gene expression wave

#### 2.1.3 Genome sequencing wave

#### 2.1.4 Big data challenge from sequencing

### 2.2 Should I take this course?

#### 2.2.1 Bioinformatics vs computational biology

#### 2.2.2 Is this class for me?

### 2.3 Course information

#### 2.3.1 Logistics

#### 2.3.2 X Shirley Liu lab introduction

### 2.4 Lab 1

**2.4.1 Introduction****2.4.2 Introduction to R****2.4.3 Introduction to Bash****2.4.4 Getting started with Cannon**

## 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 Introduction to RNA-seq experiment

4.2 RNA quality control and experimental design

4.3 Alignment

4.4 RNA-seq QC

4.5 RNA-seq expression index

4.6 RSEM and Salmon

4.7 RNA-seq read distribution

4.8 Lab 2

4.8.1 STAR tutorial

4.8.2 RSeQC tutorial

4.8.3 RSEM/Salmon Tutorial



## Chapter 5

# Differential expression, FDR, GO, and GSEA

**DESeq2** is a popular and accurate computational algorithm to detect differential gene expression from RNA-seq data. It includes many elegant quantitative considerations, such as:

- Normalize the gene read counts by library size and composition
- Model gene read counts with negative binomial distribution
- Use hierarchical modeling to stabilize the gene variance
- Use Benjamini-Hochberg to calculate control for false discovery rate of calling differentially expressed genes
- Filter lowly expressed genes to reduce the number of hypotheses to be tested

### 5.1 DESeq2 library normalization

### 5.2 DESeq2 variance stabilization

### 5.3 Multiple hypotheses testing and False Discovery Rate

## 5.4 DESeq2 gene filtering

## 5.5 Gene Ontology (GO analysis)

## 5.6 Gene Set Enrichment Analysis (GSEA)

## 5.7 DESeq2 tutorial

## Chapter 6

# Clustering

6.1 Heatmap and clustering quality

6.2 Hierarchical cluster

6.3 K means cluster

6.4 Pick K and consensus clustering

6.5 Batch effect removal

6.6 Lab3

6.6.1 PCA tutorial

6.6.2 Clustering tutorial

6.6.3 Combat tutorial

6.6.4 DESeq2 Tutorial

6.6.5 DAVID/GSEA Tutorial



## Chapter 7

# Dimension Reduction

RNA-seq samples have tens of thousands of genes, although many genes might not vary much between samples and many others have correlated gene expression. Dimension reduction techniques aim to reduce the dimension of representing each sample with tens of thousands of genes to much fewer dimensions, e.g. 2 to 100.

### 7.1 Principal Component Analysis: idea behind PCA.

PCA / SVD automatically outputs PC1, PC2, PC3, etc, with earlier PCs capturing the highest level of variability in the original data. Each PC is a linear combination of raw gene expression, and is orthogonal to all other PCs.

### 7.2 Principal Component Analysis: PCA applications.

PCA is a widely used method to project samples with high dimensions (e.g. with gene expression data) onto two dimensions for better visualization. It is an intuitive way to identify sample clusters, and identify batch effect.

### 7.3 Multidimensional Scaling (MDS)

MDS can use differential ways to calculate pair-wise distance, then use lower dimensions to satisfy the pair-wise distance. PCA is a special case of MDS.

## 7.4 Linear discriminant Analysis (LDA)

LDA is not only a dimension reduction method, but also a supervised machine learning method.



## Chapter 8

# Classification

### 8.1 Introduction

Imagine you have RNA-seq of a collection of labeled normal lung and lung cancer tissues. Given a new sample of RNA-seq from the lung with unknown diagnosis, will you be able to predict based on the existing labeled samples and the expression data whether the new sample is normal or tumor? This is a sample classification problem, and it could be solved using **unsupervised** and **supervised** learning approaches.

**Unsupervised learning** is basically clustering or dimension reduction. You can use hierarchical clustering, MDS, or PCA. After clustering and projection the data to lower dimensions, you examine the labels of the known samples (hopefully they cluster into separate groups by the label). Then you can assign label to the unknown sample based on its distance to the known samples.

**Supervised learning** considers the labels with known samples and tries to identify features that can separate the samples by the label. Cross validation is conducted to evaluate the performance of different approaches and avoid over fitting.

StatQuest has done an amazing job with machine learning with a full playlist of well organized videos. While the full playlist is worth a full course, for the purpose of the course, we will just highlight a number of widely used approaches. They include logistic regression (this is considered statistical machine learning), K nearest neighbors, random forest, and support vector machine (these are considered computer science machine learning).

### 8.2 Supervised learning

### 8.3 Cross validation

### 8.4 Regression

### 8.5 Regularization

#### 8.5.1 Ridge regression

#### 8.5.2 LASSO regression

##### 8.5.2.1 LASSO tutorial in R

### 8.6 KNN

### 8.7 Decision trees

### 8.8 Random forest

### 8.9 SVM

### 8.10 Lab 4

#### 8.10.1 K-Nearest Neighbors tutorial

#### 8.10.2 Regression/Ridge/LASSO Tutorial

#### 8.10.3 Logistic Regression Tutorial

#### 8.10.4 Support Vector Machine Tutorial

#### 8.10.5 Random Forest Tutorial

## Chapter 9

# Module I Review

9.1 Module I review

9.2 Analysis Scenario 1

9.3 Analysis Scenario 2



## 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 Motif finding in eukaryotes, and ChIP-seq

11.2 MACS and ChIP-seq QC

11.3 Identify TF interactions from ChIP-seq motifs

11.4 TF target genes and expression integration

11.5 Lab 5

11.5.1 MACS Tutorial

11.5.2 ChIP-seq QC Tutorial

11.5.3 TF Motif Finding Tutorial

11.5.4 TF Collaborator Tutorial





## Chapter 12

# Epigenetics, DNA Methylation

### 12.1 Intro to DNA Methylation

### 12.2 DNA Methylation Pattern and Function

### 12.3 DNA Methylation in Diseases

### 12.4 Techniques to Measure DNA Methylation



## Chapter 13

# Histone Modifications , Chromatin Accessibility

13.1 Nucleosome Positioning

13.2 Introduction to Histone Modifications

13.3 Infer Transcription Factor Binding from  
Histone Mark Dynamics

13.4 Using Histone Marks to Infer Gene Func-  
tions

13.5 Introduction to DNase-seq and ATAC-seq

13.6 Infer TF from Differential Genes Using  
LISA

13.7 Caution on DNase/ATAC-seq footprint  
analysis

## **13.8 Summary of Epigenetics and Chromatin**

### **13.9 Lab 6**

#### **13.9.1 ChIP-seq Expression Integration**

#### **13.9.2 Cistrome-GO Tutorial**

#### **13.9.3 ATAC-seq Analysis and LISA Tutorial**

## Chapter 14

# Hidden Markov Model

14.1 Markov Chain

14.2 Hidden Markov Model

14.3 Hidden Markov Model Forward Procedure

14.4 Hidden Markov Model Backward Procedure

14.5 HMM Forward-Backward Algorithm

14.6 Viterbi Algorithm

14.7 Baum Welch Algorithm Intuition

14.8 HMM Bioinformatics Applications



# Chapter 15

## HiC

- 15.1 Introduction to Chromatin Interaction and Organization
- 15.2 Methods to Investigate 3D Genome Organization
- 15.3 Topologically Associating Domains
- 15.4 TAD Function and Loop Anchors
- 15.5 Chromatin Compartments
- 15.6 Computational Methods to Call Chromatin Loops
- 15.7 Variations of Chromatin Interaction Technologies
- 15.8 Resources for Exploring 3D Genomes

## **15.9 Lab 7**

### **15.9.1 BS-seq and Bismark Tutorial**

### **15.9.2 Tutorial on Associating DNA Methylation with Expression**

### **15.9.3 HiC Analysis Tutorial**



## Chapter 16

# Module II Review

### 16.1 Module II Review

### 16.2 Module II Analysis Scenarios



## Chapter 17

# SNP and GWAS

### 17.1 SNP, LP, and Association Studies

### 17.2 GWAS Studies and eQTL Analysis

### 17.3 Lab 8

#### 17.3.1 HW4 FAQ & cooler

#### 17.3.2 Pikachu&HiGlass

#### 17.3.3 HMM



## Chapter 18

# GWAS and Epigenomics

18.1 Intro Functional Annotate GWAS

18.2 GWAS Functional Enrichment

18.3 Find Causal SNPs

18.4 Predict disease risk



## Chapter 19

# Single-cell RNA-seq (1)

19.1 Intro to scRNA-seq

19.2 scRNA seq techniques

19.3 scRNA seq preprocessing and QC

19.4 Cleaning up expression matrix





## Chapter 20

# Single-cell RNA-seq (2)

20.1 scRNA seq dimension reduction

20.2 Clustering and projections

20.3 Pseudo time and RNA velocity

20.4 Clustering by genotype and CITE seq



# Chapter 21

## scATAC-seq

### 21.1 Single-Cell ATAC-seq Technique

### 21.2 Single-Cell ATAC-seq Pre-Processing and QC

### 21.3 Single-Cell ATAC-seq Analysis

### 21.4 scATAC-seq Downstream Analyses and scRNA-seq Integration

### 21.5 Lab 9

#### 21.5.1 MAESTRO tutorial



## 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 Tumor Subtypes

24.2 Survival analysis

24.3 Oncogenes and Tumor Suppressor Mutations

24.4 Cancer Epigenetics

24.5 Cancer Hallmarks



## Chapter 25

# Targeted Therapy and Precision Medicine

- 25.1 Introduction to Targeted Therapy and Precision Medicine
- 25.2 Resistance to targeted therapy
- 25.3 Model system chemical and genetic screens
- 25.4 Overcoming resistance to targeted therapy



## Chapter 26

# Targeted Therapy, Drug Resistance, Compound and Genetic Screens

26.1 Hallmarks of cancer

26.2 Chemo vs targeted therapy

26.3 Drug resistance

26.4 Synthetic lethality

26.5 Precision medicine

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

26.7 Compound screens

26.8 Genetic screens

## **26.9 Tumor heterogeneity**

## Chapter 27

# Cancer Immunotherapy (1)

27.1 Systemic immunotherapy

27.2 Personalized immunotherapy

27.3 HLA and neoantigens

27.4 Tumor immune deconvolution

27.5 T cell signaling (PD1/PDL1, etc)

27.6 Other immune-cells (scRNA-seq)

27.7 Lab 10

27.7.1 TCGA exploration

27.7.2 LIMMA on microarray data

27.7.3 Survival analysis





## Chapter 28

# Cancer Immunotherapy (2)

28.1 TCR analysis

28.2 BCR analysis

28.3 Microbiome

28.4 Immunotherapy response biomarkers

28.5 Targeted therapy as immune-modulators

28.6 Epigenetic therapy as immune-modulators



## Chapter 29

# CRISPR Screens

29.1 CRISPR and KO

29.2 CRISPRa and CRISPRi

29.3 CRISPR design and outcome

29.4 CRISPR screens & DepMap

29.5 CRISPR screen analysis

29.6 CRISPR screens in drug response

29.7 CRISPR screens in immunology

29.8 Enhancer CRISPR screen

29.9 CRISPR screens + scRNA-seq



## Chapter 30

# Module IV Review and Course Review

### 30.1 Module IV Review

### 30.2 Course Review