

# Introduction to Bioinformatics and Computational Biology

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# Contents

<b>1</b>	<b>Course information</b>	<b>11</b>
1.1	Contributors . . . . .	11
<b>2</b>	<b>Introduction</b>	<b>13</b>
2.1	Brief history of bioinformatics . . . . .	14
2.2	Should I take this course? . . . . .	14
2.3	Course information . . . . .	14
2.4	Lab 1 . . . . .	14
<b>3</b>	<b>High throughput sequencing</b>	<b>15</b>
3.1	Three generations of sequencing technologies . . . . .	15
3.2	FASTQ and FASTQC . . . . .	15
3.3	Early sequence alignment (1 with 1) . . . . .	15
3.4	Sequence search algorithms (1 with many) . . . . .	16
3.5	Borrow-Wheeler Aligner (many with many) . . . . .	16
3.6	Alignment output . . . . .	16
<b>4</b>	<b>RNA-seq Quantification</b>	<b>17</b>
4.1	Introduction to RNA-seq experiment . . . . .	17
4.2	RNA quality control and experimental design . . . . .	17
4.3	Alignment . . . . .	17
4.4	RNA-seq QC . . . . .	17
4.5	RNA-seq expression index . . . . .	17
4.6	RSEM and Salmon . . . . .	17

4.7	RNA-seq read distribution . . . . .	17
4.8	Lab 2 . . . . .	17
<b>5</b>	<b>Differential expression, FDR, GO, and GSEA</b>	<b>19</b>
5.1	DESeq2 library normalization . . . . .	20
5.2	DESeq2 variance stabilization . . . . .	20
5.3	Multiple hypotheses testing and False Discovery Rate . . . . .	20
5.4	DESeq2 gene filtering . . . . .	20
5.5	Gene Ontology (GO analysis) . . . . .	20
5.6	Gene Set Enrichment Analysis (GSEA) . . . . .	20
5.7	DESeq2 tutorial . . . . .	20
<b>6</b>	<b>Clustering</b>	<b>21</b>
6.1	Heatmap and clustering quality . . . . .	21
6.2	Hierarchical cluster . . . . .	21
6.3	K means cluster . . . . .	21
6.4	Pick K and consensus clustering . . . . .	21
6.5	Batch effect removal . . . . .	21
6.6	Lab3 . . . . .	21
<b>7</b>	<b>Dimension Reduction</b>	<b>23</b>
7.1	Principal Component Analysis: idea behind PCA. . . . .	23
7.2	Principal Component Analysis: PCA applications. . . . .	23
7.3	Multidimensional Scaling (MDS) . . . . .	23
7.4	Linear discriminant Analysis (LDA) . . . . .	24
<b>8</b>	<b>Classification</b>	<b>25</b>
8.1	Introduction . . . . .	25
8.2	Supervised learning . . . . .	26
8.3	Cross validation . . . . .	26
8.4	Regression . . . . .	26
8.5	Regularization . . . . .	26
8.6	KNN . . . . .	26

<i>CONTENTS</i>	5
8.7 Decision trees . . . . .	26
8.8 Random forest . . . . .	26
8.9 SVM . . . . .	26
8.10 Lab 4 . . . . .	26
<b>9 Module I Review</b>	<b>27</b>
9.1 Module I review . . . . .	27
9.2 Analysis Scenario 1 . . . . .	27
9.3 Analysis Scenario 2 . . . . .	27
<b>10 Transcription Factor Motif Finding</b>	<b>29</b>
10.1 Transcription regulation . . . . .	29
10.2 Motif representation . . . . .	29
10.3 EM . . . . .	29
10.4 Gibbs sampler . . . . .	29
10.5 Gibbs intuition . . . . .	29
10.6 Motif finding in eukaryotes . . . . .	29
10.7 Known motif database . . . . .	29
<b>11 ChIP-seq, Expression Integration</b>	<b>31</b>
11.1 Motif finding in eukaryotes, and ChIP-seq . . . . .	31
11.2 MACS and ChIP-seq QC . . . . .	31
11.3 Identify TF interactions from ChIP-seq motifs . . . . .	31
11.4 TF target genes and expression integration . . . . .	31
11.5 Lab 5 . . . . .	31
<b>12 Epigenetics, DNA Methylation</b>	<b>33</b>
12.1 Intro to DNA Methylation . . . . .	33
12.2 DNA Methylation Pattern and Function . . . . .	33
12.3 DNA Methylation in Diseases . . . . .	33
12.4 Techniques to Measure DNA Methylation . . . . .	33

<b>13 Histone Modifications , Chromatin Accessibility</b>	<b>35</b>
13.1 Nucleosome Positioning . . . . .	36
13.2 Introduction to Histone Modifications . . . . .	36
13.3 Infer Transcription Factor Binding from Histone Mark Dynamics	36
13.4 Using Histone Marks to Infer Gene Functions . . . . .	36
13.5 Introduction to DNase-seq and ATAC-seq . . . . .	36
13.6 Infer TF from Differential Genes Using LISA . . . . .	36
13.7 Caution on DNase/ATAC-seq footprint analysis . . . . .	36
13.8 Summary of Epigenetics and Chromatin . . . . .	36
13.9 Lab 6 . . . . .	36
<b>14 Hidden Markov Model</b>	<b>37</b>
14.1 Markov Chain . . . . .	37
14.2 Hidden Markov Model . . . . .	37
14.3 Hidden Markov Model Forward Procedure . . . . .	37
14.4 Hidden Markov Model Backward Procedure . . . . .	37
14.5 HMM Forward-Backward Algorithm . . . . .	37
14.6 Viterbi Algorithm . . . . .	37
14.7 Baum Welch Algorithm Intuition . . . . .	37
14.8 HMM Bioinformatics Applications . . . . .	37
<b>15 HiC</b>	<b>39</b>
15.1 Introduction to Chromatin Interaction and Organization . . . . .	40
15.2 Methods to Investigate 3D Genome Organization . . . . .	40
15.3 Topologically Associating Domains . . . . .	40
15.4 TAD Function and Loop Anchors . . . . .	40
15.5 Chromatin Compartments . . . . .	40
15.6 Computational Methods to Call Chromatin Loops . . . . .	40
15.7 Variations of Chromatin Interaction Technologies . . . . .	40
15.8 Resources for Exploring 3D Genomes . . . . .	40
15.9 Lab 7 . . . . .	40

<i>CONTENTS</i>	7
<b>16 Module II Review</b>	<b>41</b>
16.1 Module II Review . . . . .	41
16.2 Module II Analysis Scenarios . . . . .	41
<b>17 SNP and GWAS</b>	<b>43</b>
17.1 SNP, LP, and Association Studies . . . . .	43
17.2 GWAS Studies and eQTL Analysis . . . . .	43
<b>18 GWAS and Epigenomics</b>	<b>45</b>
18.1 Find tissue / cell type . . . . .	45
18.2 Identify causal SNPs and genes . . . . .	45
18.3 Predict phenotypes . . . . .	45
<b>19 Single-cell RNA-seq (1)</b>	<b>47</b>
19.1 Intro to scRNA-seq . . . . .	47
19.2 Smart, Droplet, microwell, SCI-based . . . . .	47
19.3 QC . . . . .	47
19.4 Normalization . . . . .	47
19.5 Imputation . . . . .	47
19.6 Dimension reduction . . . . .	47
19.7 Clustering . . . . .	47
19.8 t-SNE and UMAP . . . . .	47
<b>20 Single-cell RNA-seq (2)</b>	<b>49</b>
20.1 Annotate scRNA-seq clusters . . . . .	49
20.2 Differential expression . . . . .	49
20.3 Batch effect removal . . . . .	49
20.4 Pseudotime . . . . .	49
20.5 Overload 10X . . . . .	49
20.6 Other applications (CITE-seq, multi-seq, spatial transcriptomics)	49

<b>21 scATAC-seq</b>	<b>51</b>
21.1 Intro to scATAC-seq . . . . .	51
21.2 Sample and cell QC . . . . .	51
21.3 Dimension reduction, clustering & visualization . . . . .	51
21.4 Differential peaks and annotations . . . . .	51
21.5 Integration with scRNA-seq . . . . .	51
<b>22 Module III Review</b>	<b>53</b>
22.1 Module III Review . . . . .	53
<b>23 Cancer Genome Sequencing , Mutation analyses</b>	<b>55</b>
23.1 Intro to TCGA . . . . .	55
23.2 Cancer mutation characterization . . . . .	55
23.3 Cancer mutation patterns . . . . .	55
23.4 Tumor purity and clonality . . . . .	55
23.5 Interpret tumor mutations . . . . .	55
23.6 Find cancer genes . . . . .	55
23.7 Summary and future . . . . .	55
<b>24 Cancer Subtyping, Survival Analyses</b>	<b>57</b>
24.1 TCGA expression . . . . .	57
24.2 Tumor subtypes . . . . .	57
24.3 Survival analysis . . . . .	57
24.4 GoF Oncogenes and LoF TS . . . . .	57
24.5 Chromatin regulator mutations in cancer . . . . .	57
24.6 DNA methylation and CIMP . . . . .	57
<b>25 Targeted Therapy, Drug Resistance, Compound and Genetic Screens</b>	<b>59</b>
25.1 Hallmarks of cancer . . . . .	60
25.2 Chemo vs targeted therapy . . . . .	60
25.3 Drug resistance . . . . .	60
25.4 Synthetic lethality . . . . .	60



<i>CONTENTS</i>	9
25.5 Precision medicine . . . . .	60
25.6 Tumor (bulk vs scRNA-seq), mice, cell lines . . . . .	60
25.7 Compound screens . . . . .	60
25.8 Genetic screens . . . . .	60
25.9 Tumor heterogeneity . . . . .	60
<b>26 Cancer Immunotherapy (1)</b>	<b>61</b>
26.1 Systemic immunotherapy . . . . .	61
26.2 Personalized immunotherapy . . . . .	61
26.3 HLA and neoantigens . . . . .	61
26.4 Tumor immune deconvolution . . . . .	61
26.5 T cell signaling (PD1/PDL1, etc) . . . . .	61
26.6 Other immune-cells (scRNA-seq) . . . . .	61
<b>27 Cancer Immunotherapy (2)</b>	<b>63</b>
27.1 TCR analysis . . . . .	63
27.2 BCR analysis . . . . .	63
27.3 Microbiome . . . . .	63
27.4 Immunotherapy response biomarkers . . . . .	63
27.5 Targeted therapy as immune-modulators . . . . .	63
27.6 Epigenetic therapy as immune-modulators . . . . .	63
<b>28 CRISPR Screens</b>	<b>65</b>
28.1 CRISPR and KO . . . . .	65
28.2 CRISPRa and CRISPRi . . . . .	65
28.3 CRISPR design and outcome . . . . .	65
28.4 CRISPR screens & DepMap . . . . .	65
28.5 CRISPR screen analysis . . . . .	65
28.6 CRISPR screens in drug response . . . . .	65
28.7 CRISPR screens in immunology . . . . .	65
28.8 Enhancer CRISPR screen . . . . .	65
28.9 CRISPR screens + scRNA-seq . . . . .	65

<b>29 Module IV Review and Course Review</b>	<b>67</b>
29.1 Module IV Review . . . . .	67
29.2 Course Review . . . . .	67

# 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



## 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**