



3000788 Intro to Comp Molec Biol

Lecture 1: Course introduction and logistics

August 17, 2023



Sira Sriswasdi, PhD

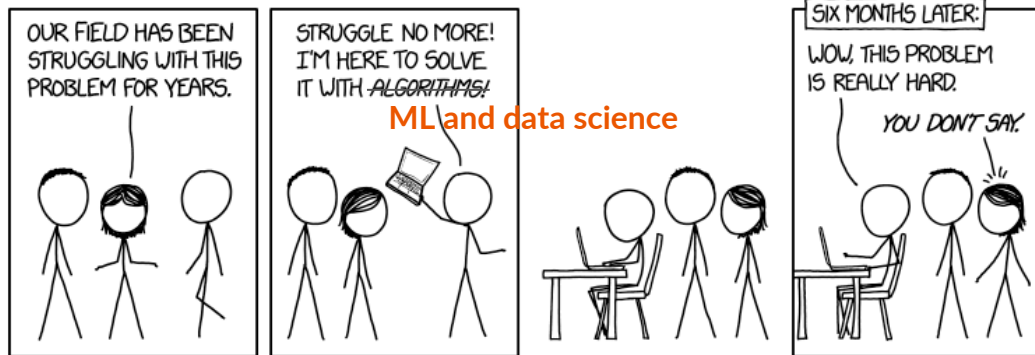
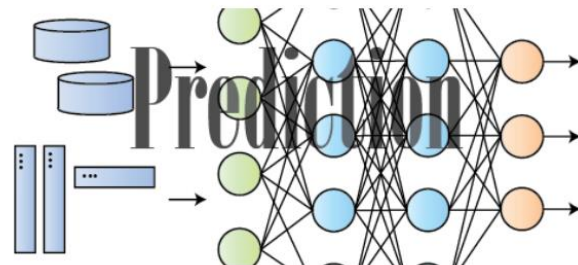
- Research Affairs
- Center of Excellence in Computational Molecular Biology (CMB)
- Center for Artificial Intelligence in Medicine (CU-AIM)



About instructor



$$\begin{aligned}
 &+ A \sum_{s=0}^{\infty} \sum_{t=0}^{\infty} \sum_{m=0}^{d-1} s \cdot B^t \cdot \mathbf{1}_{m \leq s < t} \cdot p_s^{t-s} \\
 &+ A \sum_{s=0}^{\infty} \sum_{t=0}^{\infty} \sum_{m=0}^{d-1} s \cdot B^t \cdot \mathbf{1}_{m < s \leq t} \cdot \binom{t-s+k-1}{k-1} \cdot p_s^{t-s} (1-p_s)^k \\
 &+ A \sum_{s=0}^{\infty} \sum_{t=0}^{\infty} \sum_{m=0}^{d-1} s \cdot B^t \cdot \mathbf{1}_{m < s \leq t} \cdot \mathbf{1}_{r > m} \cdot \binom{t-s+k-1}{k} \cdot p_s^{t-s} (1-p_s)^{k+1} \\
 \sum_{s=-n}^{\infty} \sum_{t=-n}^{\infty} \sum_{m=-n}^{d-1} s \cdot B^t \cdot \mathbf{1}_{m \geq s=t} &= \sum_{s=-n}^{d-1} \sum_{t=-n}^m t \cdot B^t
 \end{aligned}$$



Credit: "Here to Help" from xkcd comic, reprinted under Creative Commons License

- BS in Mathematics
- PhD in Computational Biology

Keywords

- Biological Networks
- Proteomics / Mass Spectrometry
- Molecular Evolution

About you



Please introduce yourself

- Name & nickname
- Graduate program & year
- Undergraduate background
- Research interest
- Thesis advisor & topic (if you already picked)

About this course



- Survey broad topics in computational molecular biology
- Always ask “Why?”
- Theory and practice
- Standard & customized bioinformatics workflow
- Python programming
- Machine learning & data science

Course structure

Module	Date	Topics	Assignment
1	9 Aug – 16 Aug	Introduction & statistics	Problem set 1
2	23 Aug – 6 Sep	DNA sequencing & applications	Problem set 2
3	8 Sep – 22 Sep	Transcriptomics	Problem set 3-4
4	27 Sep – 25 Oct	Advanced topics - Single-cell data - Proteomics - Chromatin organization - Biological networks	Problem set 5-7
5	27 Oct – 15 Nov	Python skills for statistical analysis and visualization	Problem set 8-9
6	17 Nov – 24 Nov	Machine learning & applications	Problem set 10
7	29 Nov	Systems biology	
8	1 Dec	Final	Presentation

Grading criteria



- Problem set [8% x 10 problem sets]
 - Can work with each other
 - Write your own answer
- Final presentation [10%]
 - Present one article in computational biology
 - One with older approach and one with newer approach
 - Compare & discuss
- In-class activity [10%]
 - Hands-on practice
 - Discussion

Kaggle's programming

≡ kaggle

+ Create

🏠 Home

🏆 Competitions

📁 Datasets

<> Code

💬 Discussions

🎓 Courses

▼ More

🔍 Search

📚 Explore Courses



Intro to Programming

Get started with Python, if you have no coding experience.



Python

Learn the most important language for data science.



Intro to Machine Learning

Learn the core ideas in machine learning, and build your first models.



Pandas

Solve short hands-on challenges to perfect your data manipulation skills.



Intermediate Machine Learning

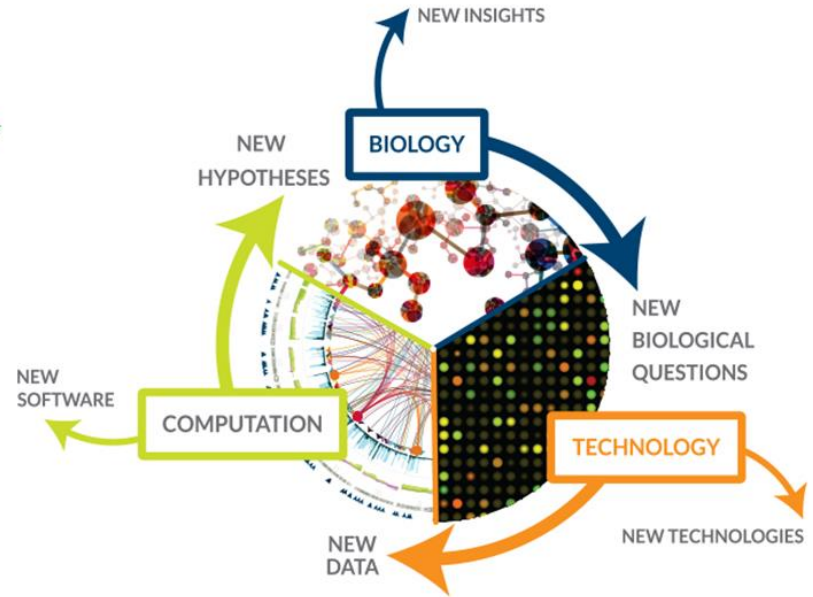
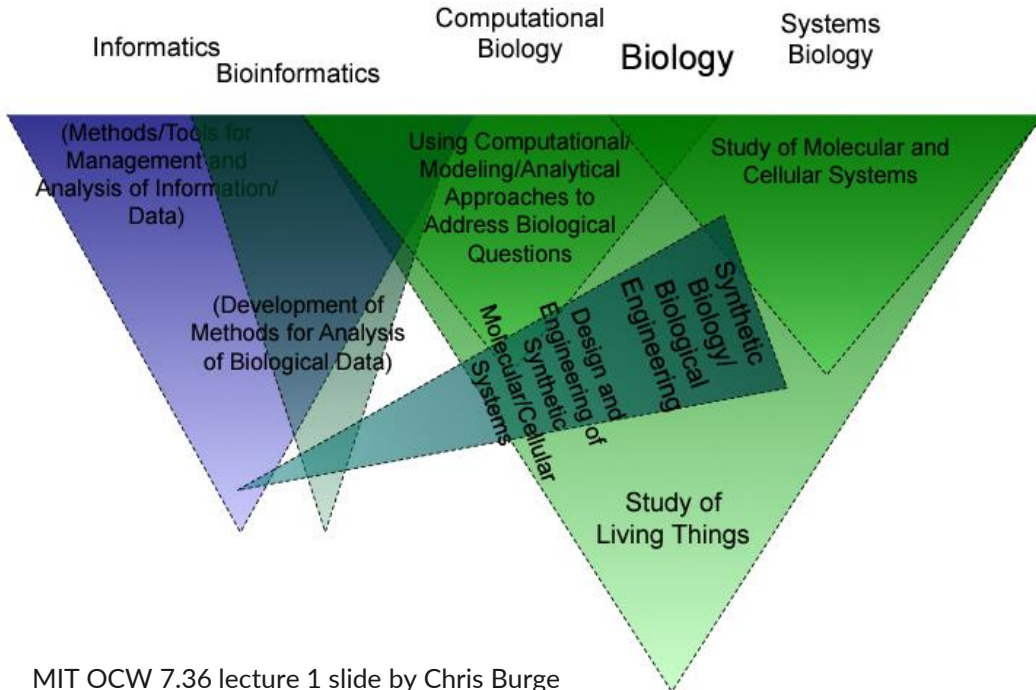
Handle missing values, non-numeric values, data leakage, and more.



Data Visualization

Make great data visualizations. A great way to see the power of coding!

What is computational biology?



Biology-inspired motif analysis



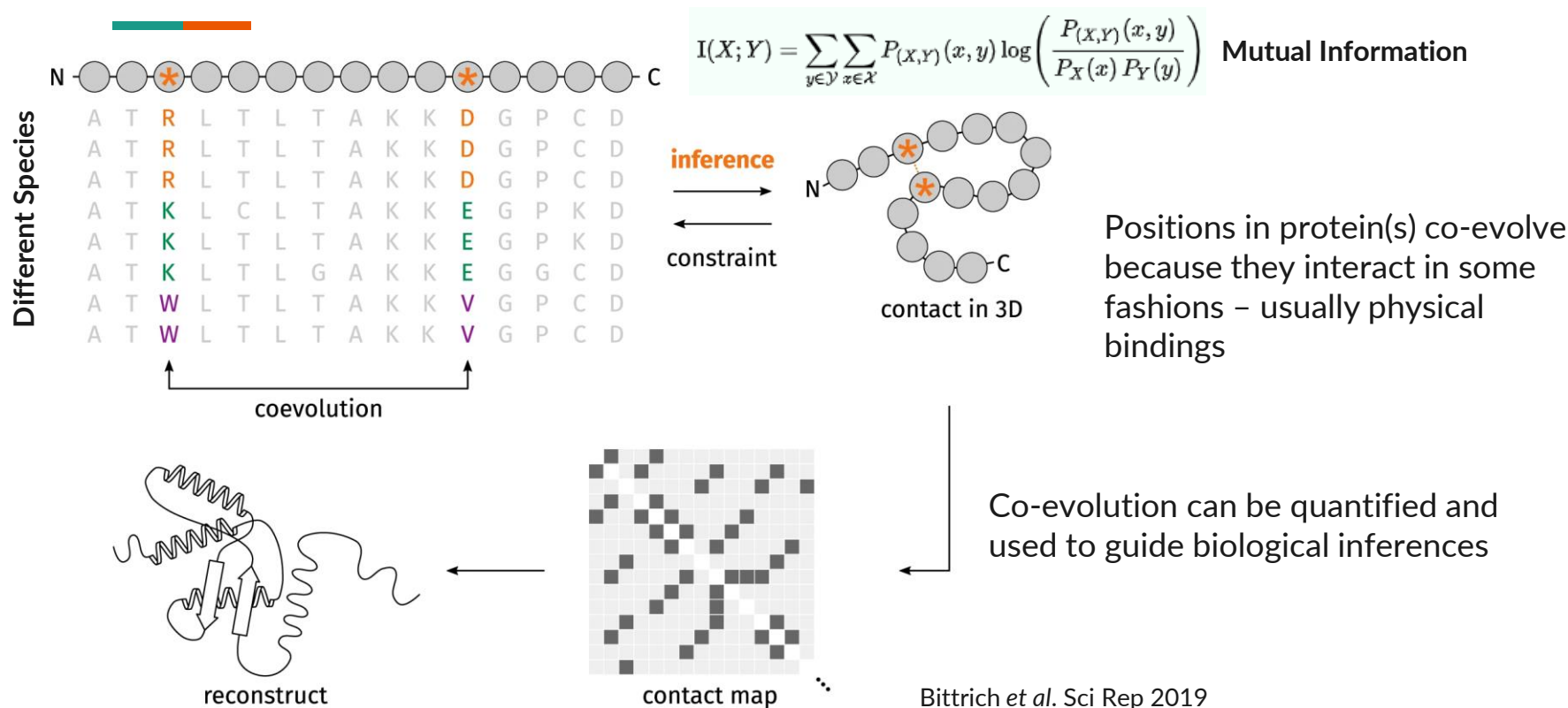
How to identify the motif?

Experiment can isolate DNA sites with bound protein
Gibbs Sampling to identify similar patterns

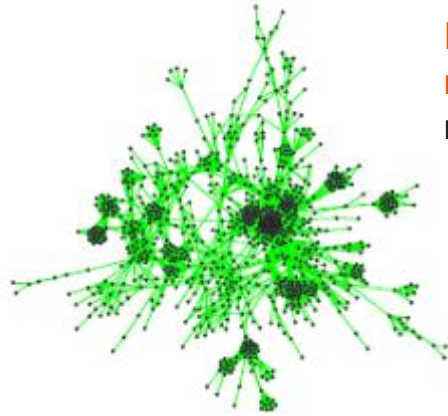


CGGGGCTATcCAgCTGGGTCGTCACATTCCCCTT
TTTGAGGGTGCCCAATAAggGCAACTCCAAAGCGGACAAA
GGATGgAtCTGATGCCGTTTGACGACCTA
AAGGAAaGCAACcCCAGGAGCGCCTTTGCTGG
AGATTATAATGTCGGTCCtTGgAACTTC
CAACTGAGATCATGCTGCATGCcAtTTTCAAC
TACATGATCTTTTGATGgcACTTGGATGAGGGAATGATGC

Capturing co-evolution with mutual information



Using graph theory to study biological networks

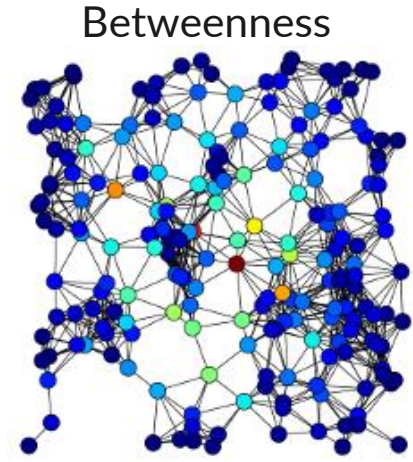
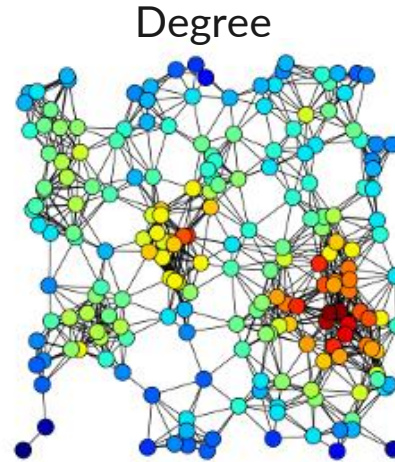


Proteins involved in
many interactions
might be important

Proteins that connect
other proteins might
be important

Node = Protein

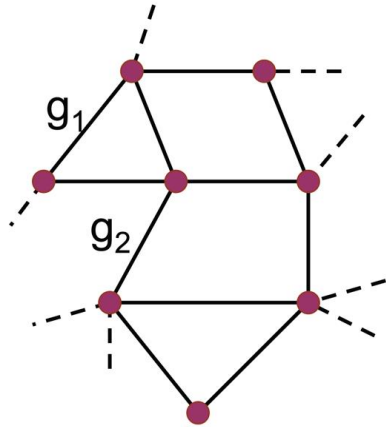
Edge = Protein-protein interaction



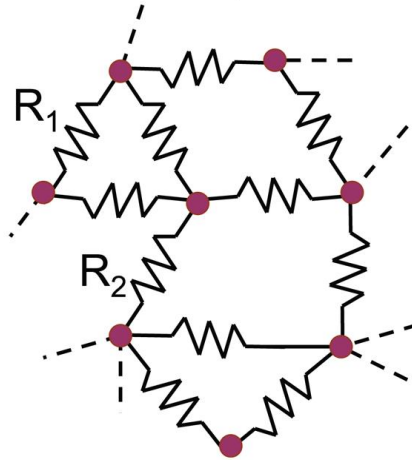
Images from wikipedia

Electrical circuit model for biological signal flows

Interactome network



Circuit representation



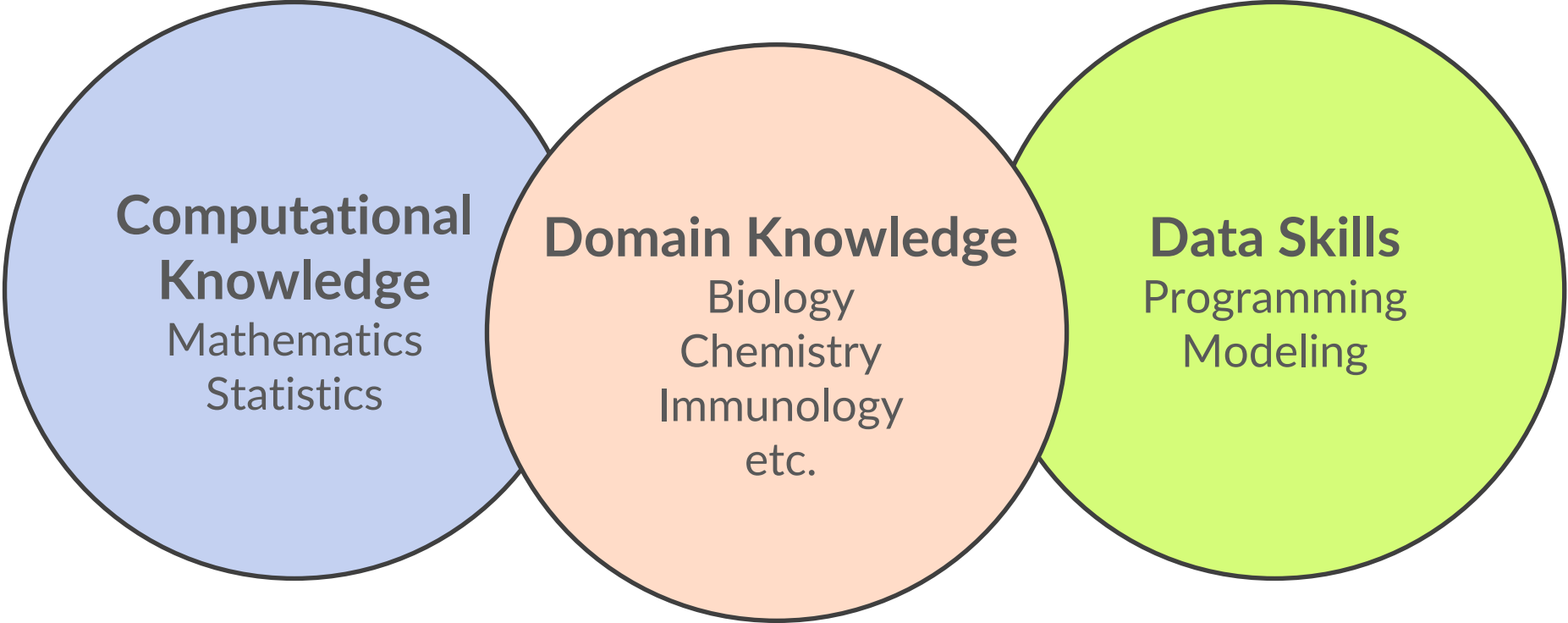
- protein
- protein-protein interaction
- g_n interaction confidence score
- R_n resistance

Missiuro et al. PLOS Comp Biol 2009

To determine how information flows between two nodes

Apply Kirchoff's laws to calculate the current through the circuit

Course objectives



**Computational
Knowledge**
Mathematics
Statistics

Domain Knowledge
Biology
Chemistry
Immunology
etc.

Data Skills
Programming
Modeling

Knowledge enables communication



Module 1: Statistics



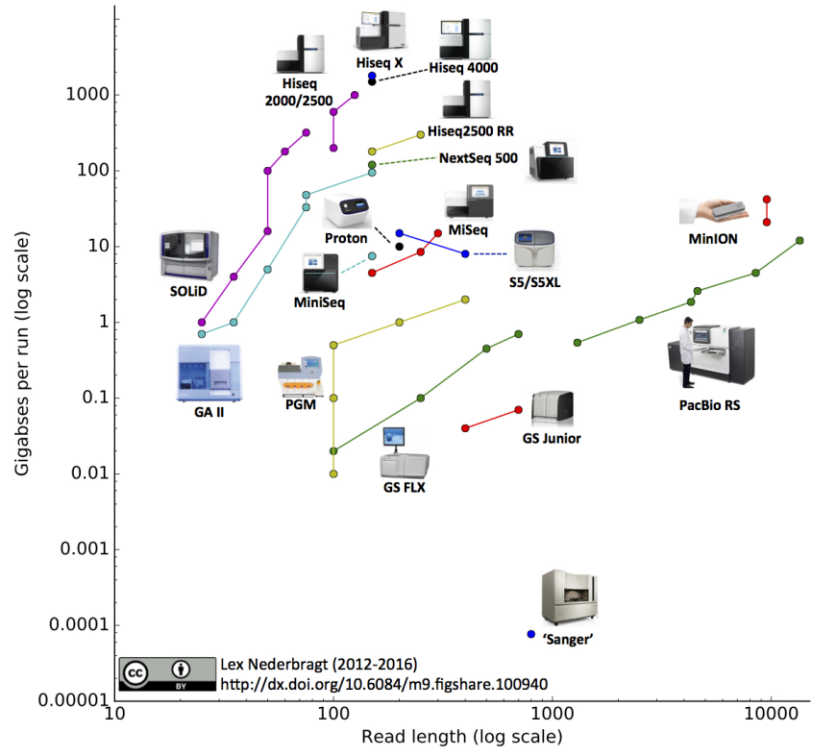
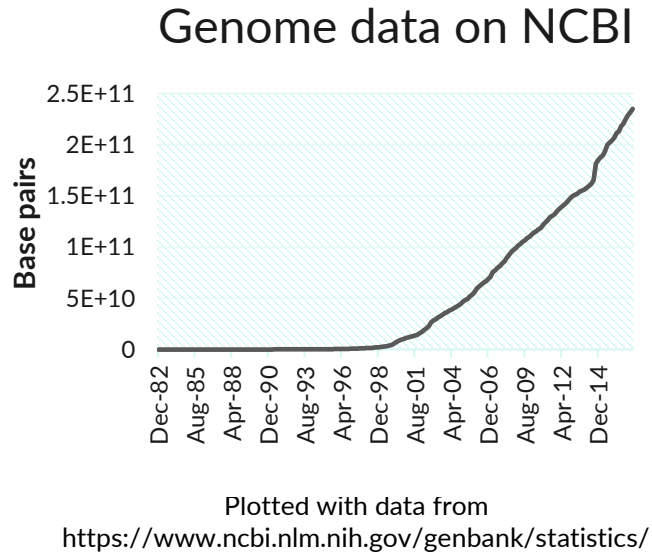
- P-values help distinguish biological pattern from random chance
 - Differential test of gene expression
 - Enrichment of biological function terms among differentially expressed genes
- How were they calculated?
 - Null hypothesis
 - Correction for multiple testing
- Which test to use?
 - Paired and unpaired t -tests
 - What about Mann-Whitney U? Wilcoxon rank-sum? Sign test?
 - Likelihood ratio test & maximum likelihood principle
 - Permutation test

Module 2: DNA sequencing & applications

- What do you think kickstarted modern-day computational biology?
- First draft of human genome, 26 June 2000
 - BLAST sequence alignment
- Gene structure annotation
 - Exome sequencing
 - Oligo nucleotide microarray

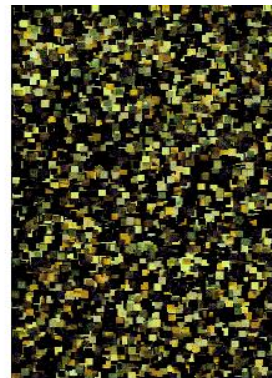


Improvements in DNA sequencing

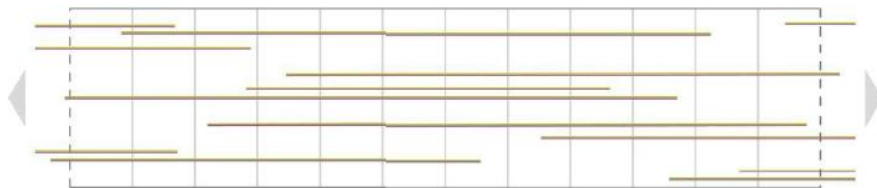


Combining short read and long read data

Short Reads



Long Reads



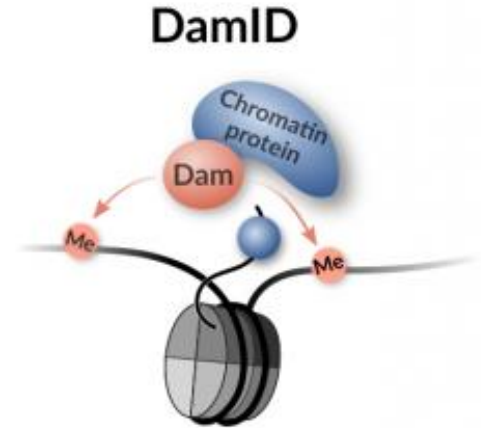
Power of long-read techniques



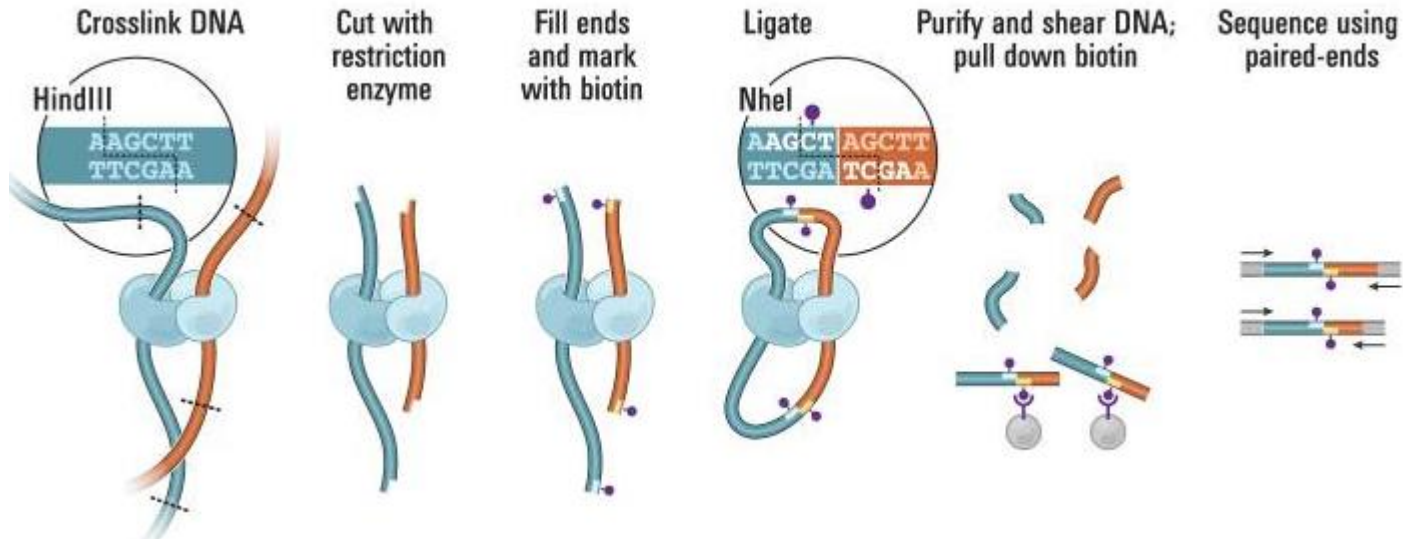
- How long is long?
- More than A/T/C/G sequencing
- Resolving isoforms and haplotypes
- Resolving repetitive genomic regions
- No DNA amplification

DNA sequencing applications

- Bisulfite-seq
 - DNA methylation
- ChIP-seq, DamID-seq
 - Histone modification, DNA-binding protein
- DNase-seq, MNase-seq, ATAC-seq
 - DNA accessibility
- 3C, 4C, 5C, Hi-C, ChIA-PET
 - Chromatin folding structure

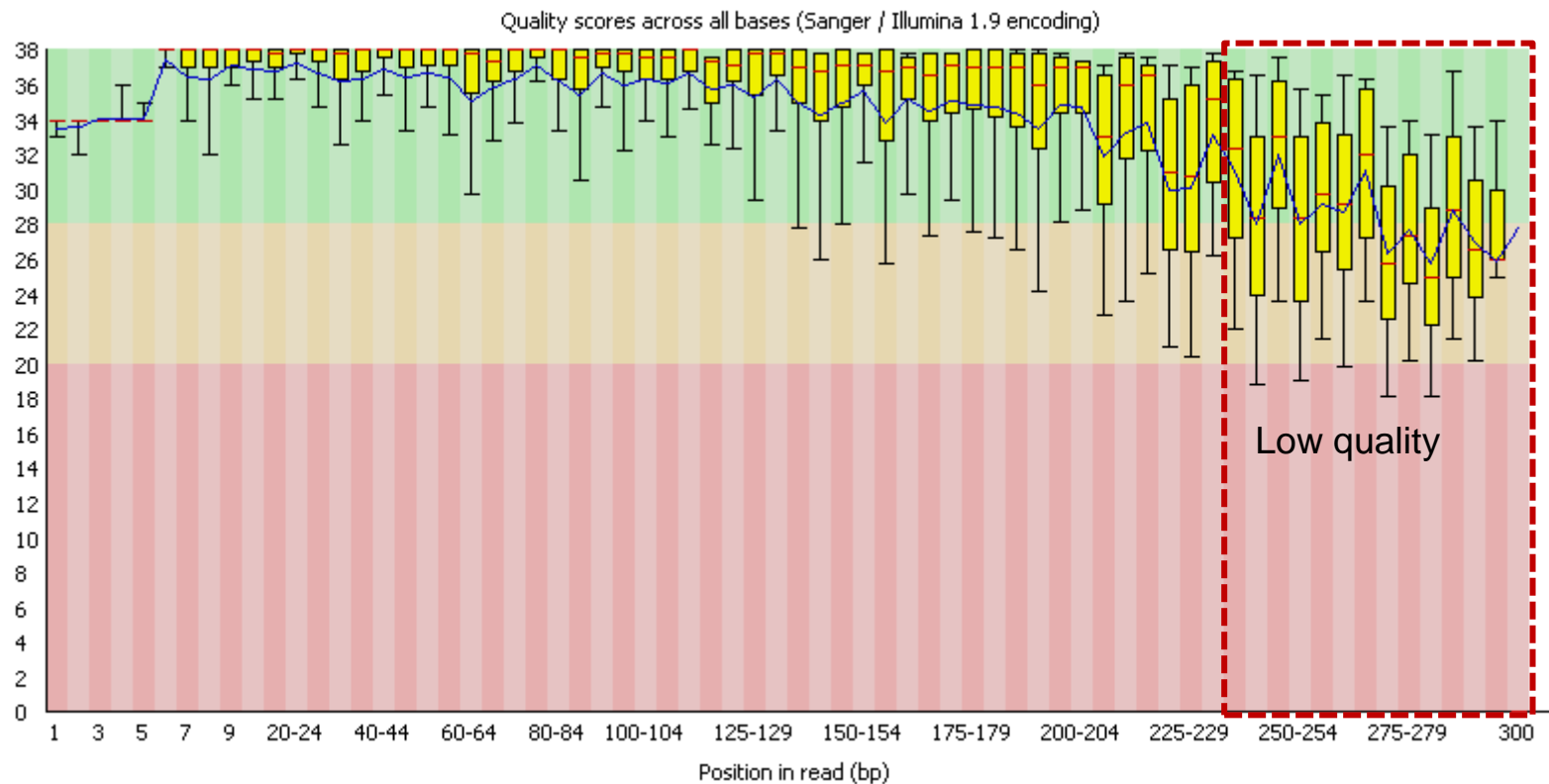


Hi-C: Chromatin folding structure



Lieberman-Aiden *et al.* Science 2009

DNA sequencing QC



Important file formats

```
Coor      12345678901234  5678901234567890123456789012345
ref       AGCATGTTAGATAA**GATAGCTGTGCTAGTAGGCAGTCAGCGCCAT

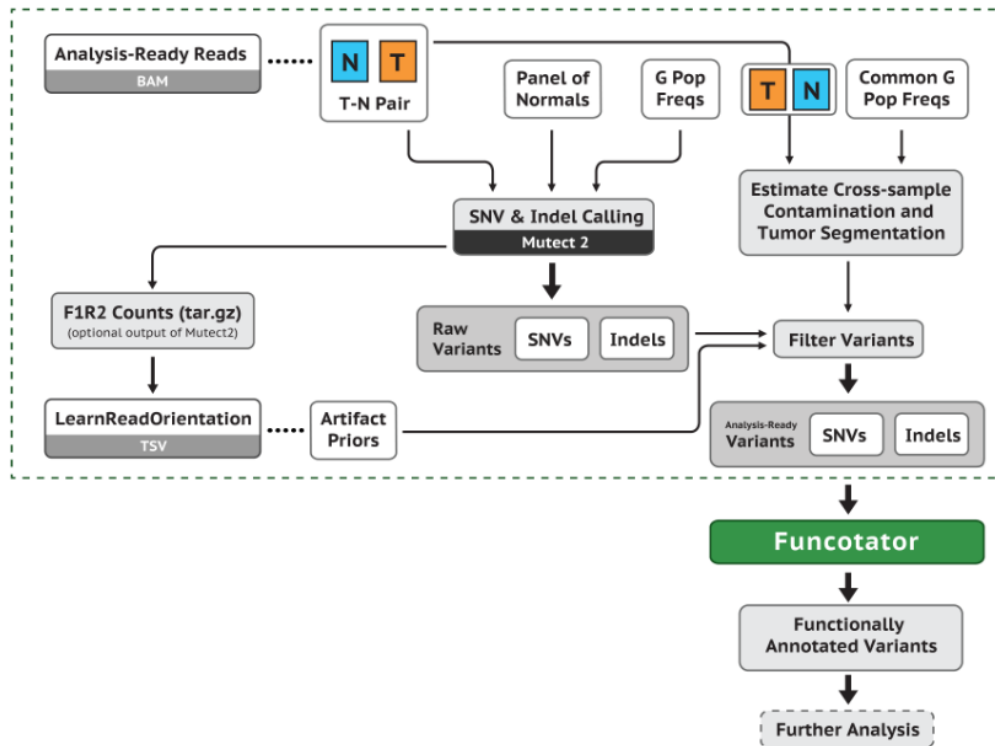
+r001/1      TTAGATAAAGGATA*CTG
+r002      aaaAGATAA*GGATA
+r003      gcctaAGCTAA
+r004      ATAGCT.....TCAGC
-r003      ttagctTAGGC
-r001/2      CAGCGGCAT
```

The corresponding SAM format is:¹

```
@HD VN:1.5 SO:coordinate
@SQ SN:ref LN:45
r001  99 ref  7 30 8M2I4M1D3M = 37 39 TTAGATAAAGGATACTG *
r002   0 ref  9 30 3S6M1P1I4M * 0 0 AAAAGATAAGGATA *
r003   0 ref  9 30 5S6M * 0 0 GCCTAAGCTAA * SA:Z:ref,29,-,6H5M,17,0;
r004   0 ref 16 30 6M14N5M * 0 0 ATAGCTTCAGC *
r003 2064 ref 29 17 6H5M * 0 0 TAGGC * SA:Z:ref,9,+,5S6M,30,1;
r001 147 ref 37 30 9M = 7 -39 CAGCGGCAT * NM:i:1
```

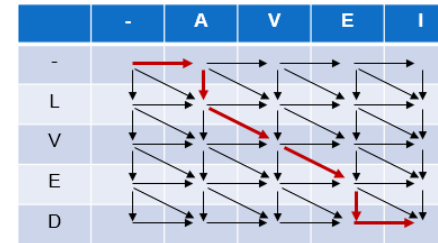
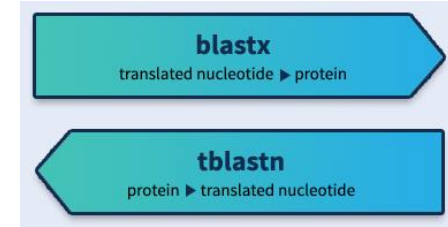
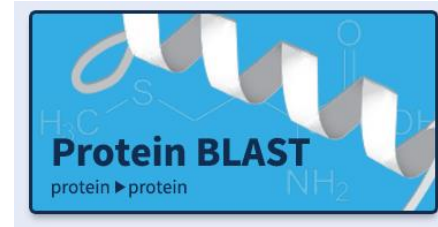
- SAM, BAM, BED, GTF, GFF, FASTA, FASTQ, VCF, MAF

GATK variant calling pipelines

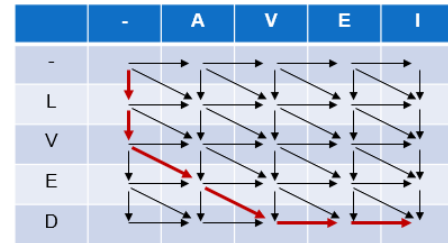


Basic Local Alignment Search Tool (BLAST)

- How does it work?
 - How should we adjust its parameters?
- What questions can it answer?
 - Functional annotation
 - Taxonomy annotation
 - A start for evolutionary analysis
- Variants of BLAST
 - MEGABLAST
 - PSI-BLAST



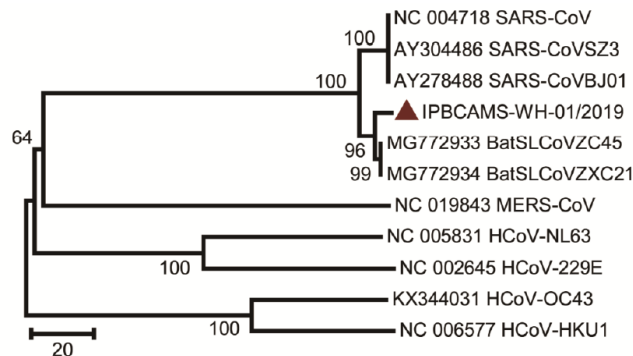
↑
A - V E - I
- L V E D -



↑
- - A V E I
L V E D - -

Phylogenetics

- Evolution is informative
- So many parameters and models
 - How to properly analyze?
 - Which tools to use?



Guo et al. Clin Infect Dis (2020)

MX: Analysis Preferences

Phylogeny Reconstruction

Option	Setting
ANALYSIS	
Statistical Method →	Maximum Likelihood
PHYLOGENY TEST	
Test of Phylogeny →	None
No. of Bootstrap Replications →	None
	Bootstrap method
SUBSTITUTION MODEL	
Substitutions Type →	Nucleotide
Model/Method →	Tamura-Nei model
RATES AND PATTERNS	
Rates among Sites →	Uniform Rates
No of Discrete Gamma Categories →	Not Applicable
DATA SUBSET TO USE	
Gaps/Missing Data Treatment →	Use all sites
Site Coverage Cutoff (%) →	Not Applicable
TREE INFERENCE OPTIONS	
ML Heuristic Method →	Nearest-Neighbor-Interchange (NNI)
Initial Tree for ML →	Make initial tree automatically (Default - NJ/BioNJ)
Initial Tree File →	Not Applicable
Branch Swap Filter →	None
SYSTEM RESOURCE USAGE	
Number of Threads →	7

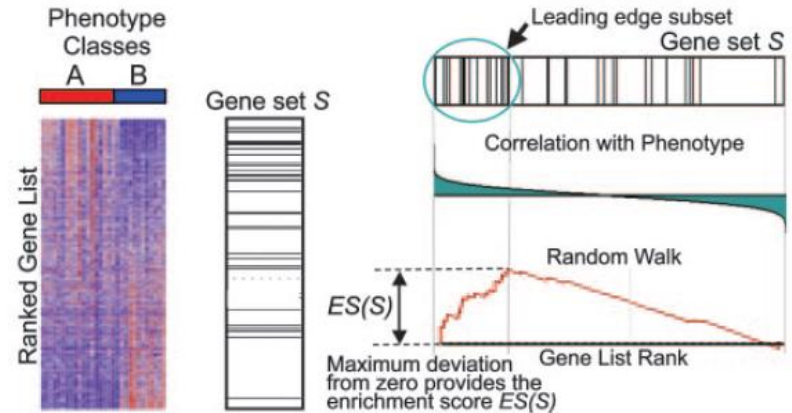
Module 3: Transcriptomics



- Microarray vs RNA-seq vs Nanostring
 - Different data models and computational analyses
- Pseudoalignment of RNA-seq
 - kallisto, salmon
- StringTie's hybrid alignment and *de novo* assembly pipeline
- Pairing RNA-seq processing and differential expression analysis tools
 - HTSeq-count with DESeq2
 - salmon with sleuth

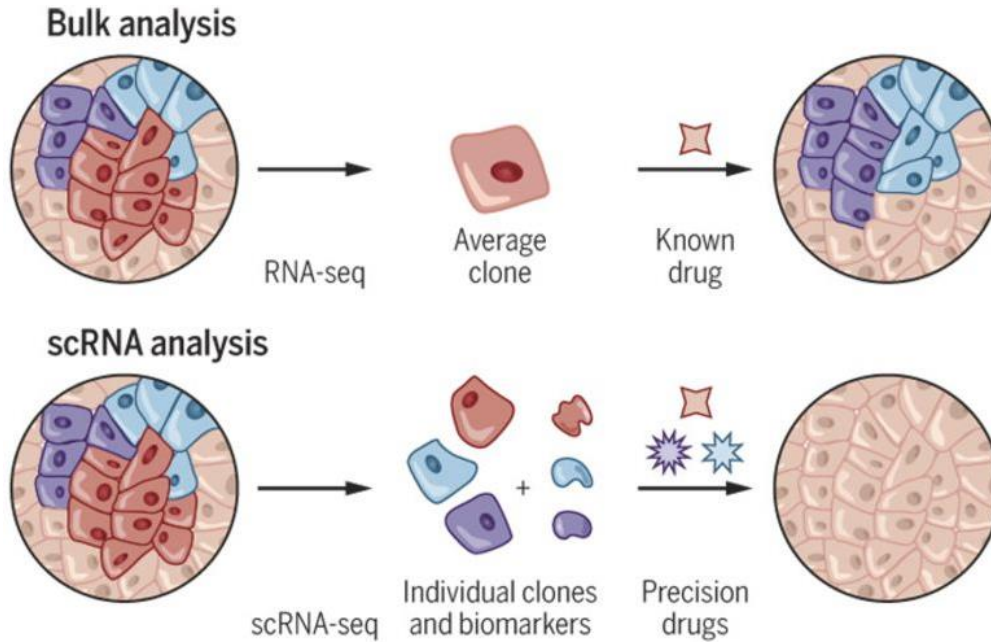
Functional enrichment analysis

- Overrepresentation analysis
 - Frequent functional terms
 - Hypergeometric distribution
- Gene set enrichment analysis (GSEA)
 - Random walk model
- Gene-gene network topology
 - Frequent functional terms
 - Nearby gene on network

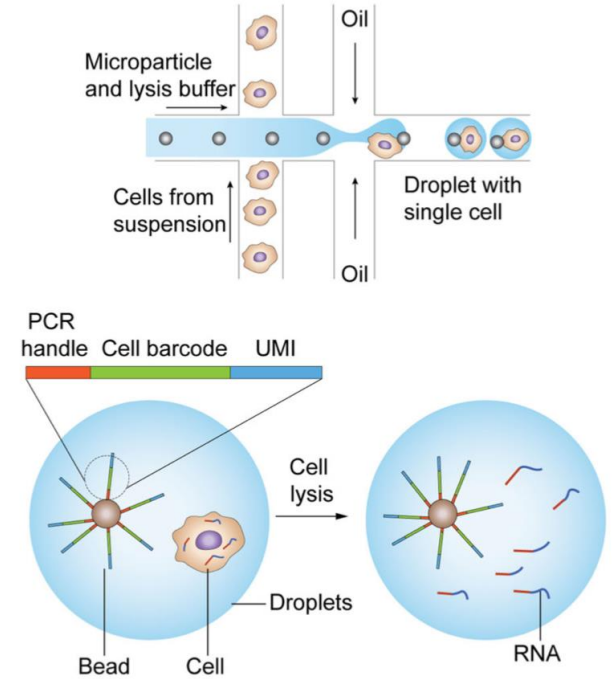


Subramanian *et al.* PNAS. 102:15545-15550 (2005)

Module 4: Advanced topics

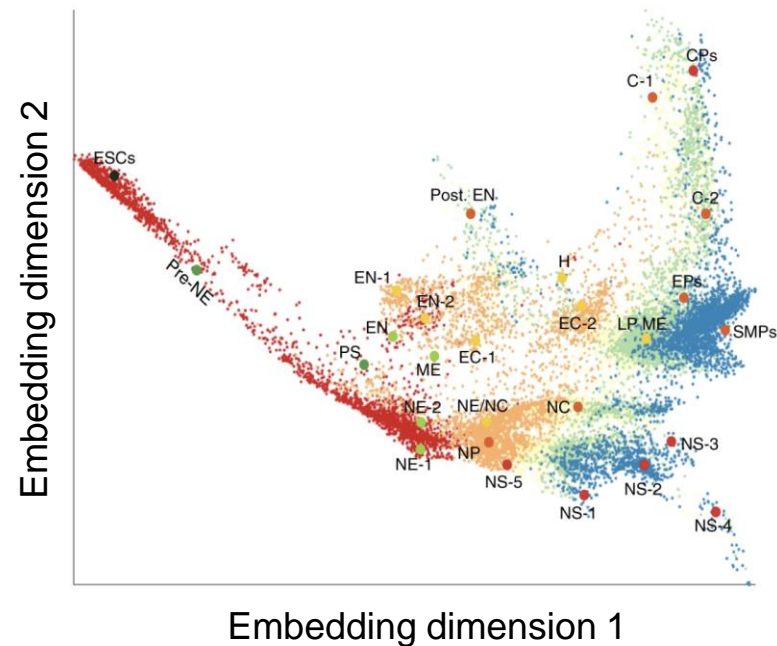
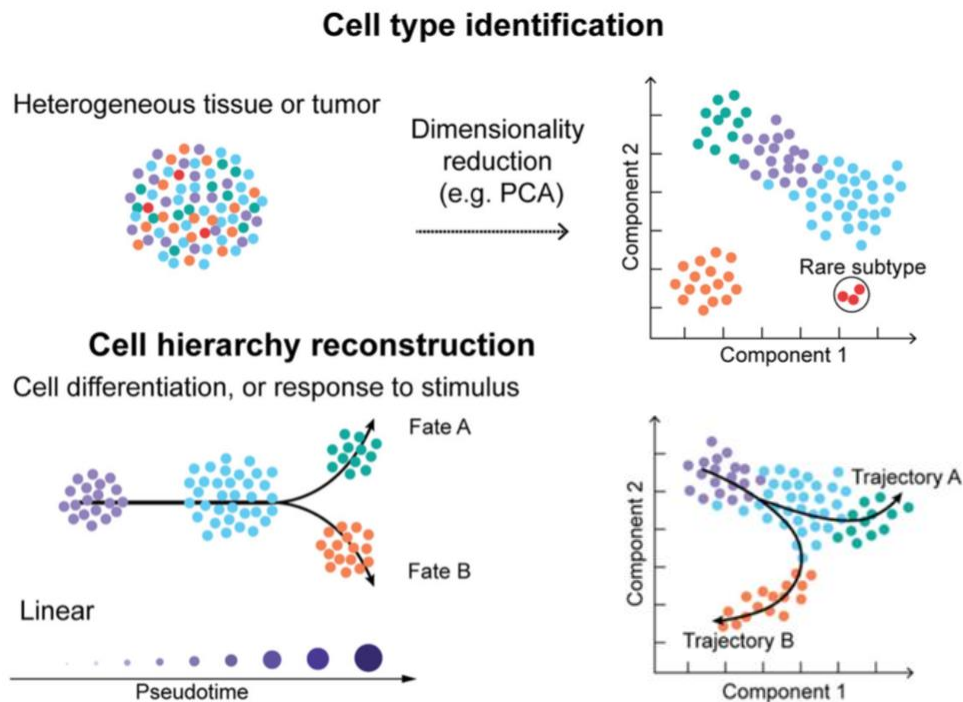


Shalek and Benson. Science Trans Med. 9:eaan4730 (2017)

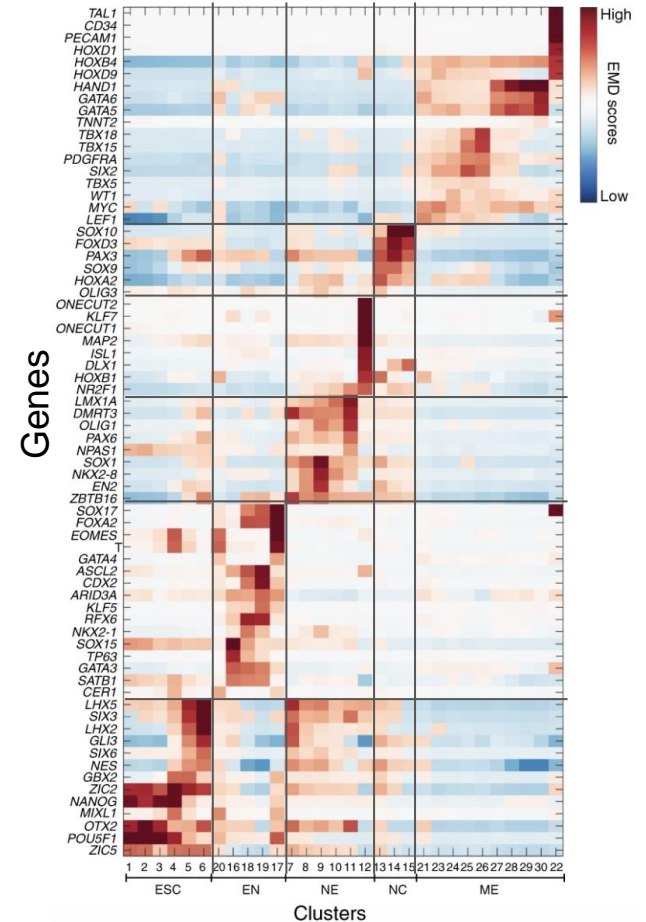
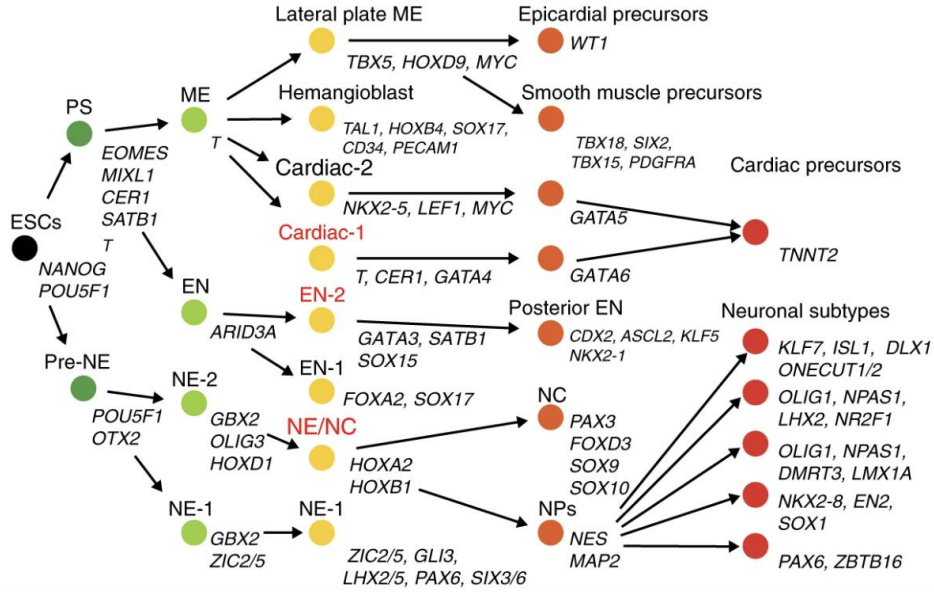


Hwang *et al.* Exp & Mol Med 50:96 (2018)

Power of single-cell data



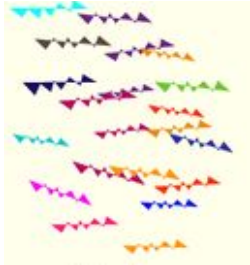
Power of single-cell data



Source: Moon et al. Nature Biotechnology 37:1482-92 (2019)

Proteomics & mass spectrometry

Peptides mixture



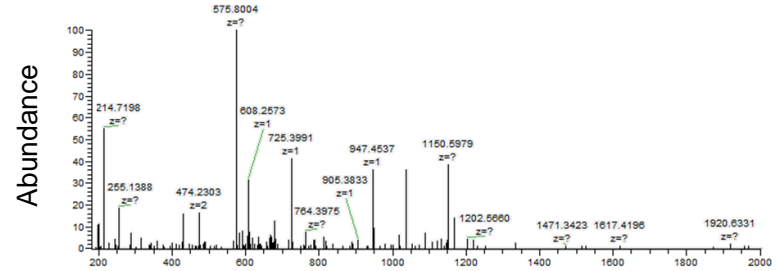
Mass spectrometer



Image from planetorbitrap.com



Peptide mass spectrum

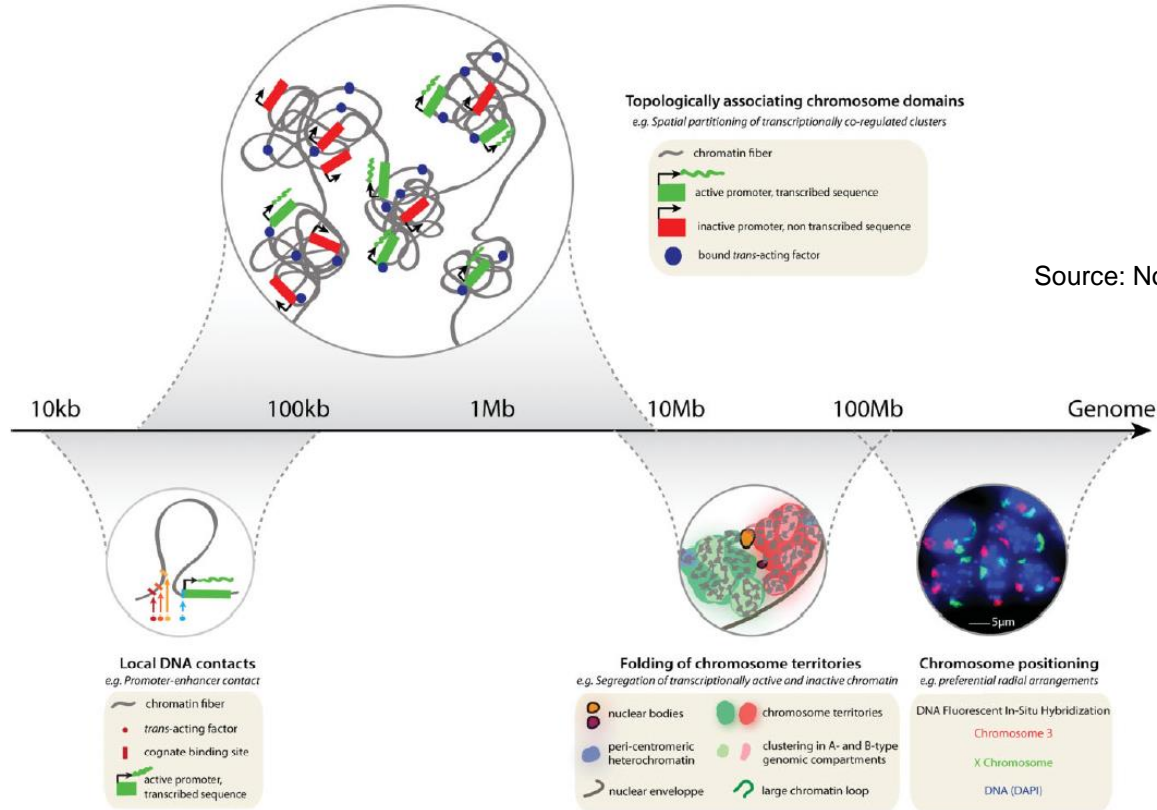


Mass/Charge



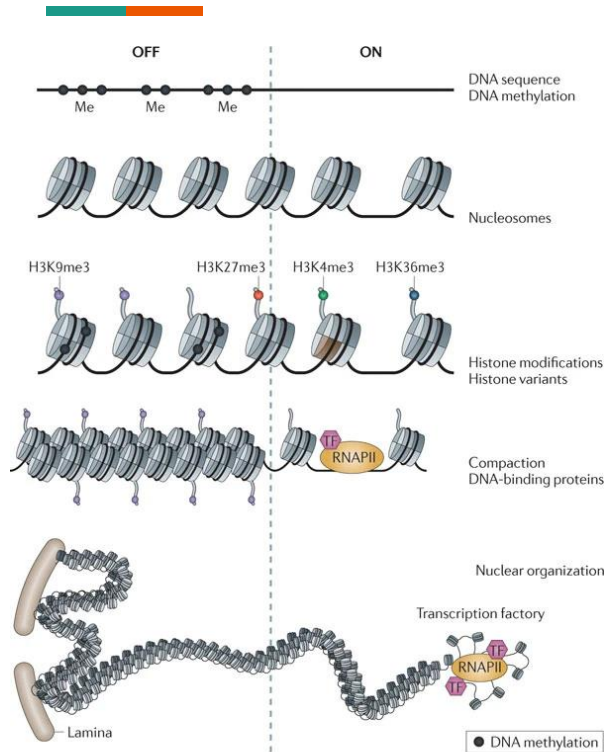
SAPYSAMIADQVAQR

Chromatin organization

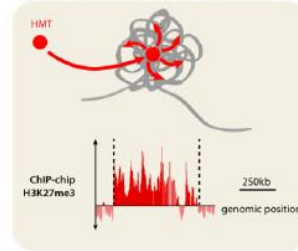


Source: Nora *et al.* Bioessay (2013)

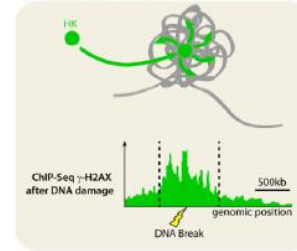
Epigenetics and gene expression regulation



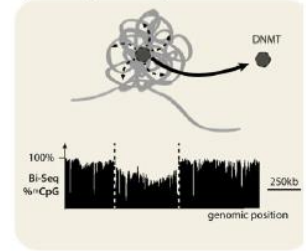
A) Blocks of H3K27me3 or H3K9me2/3



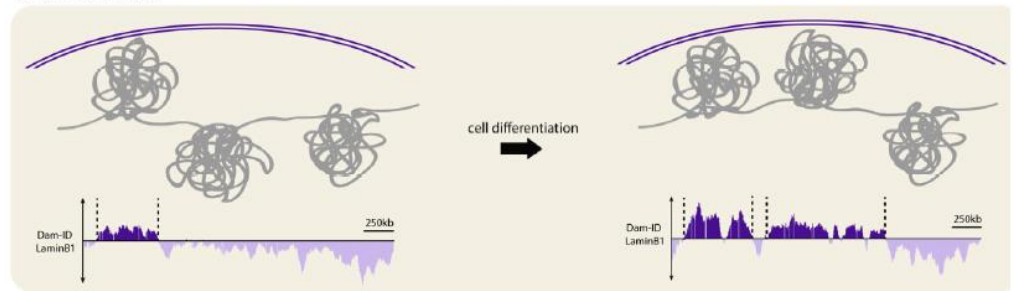
B) Domains of γ -H2AX



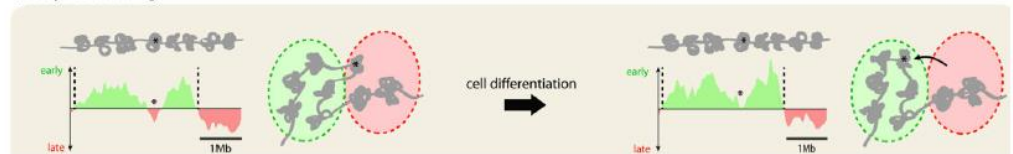
C) Partially DNA methylated domains



D) Lamina association

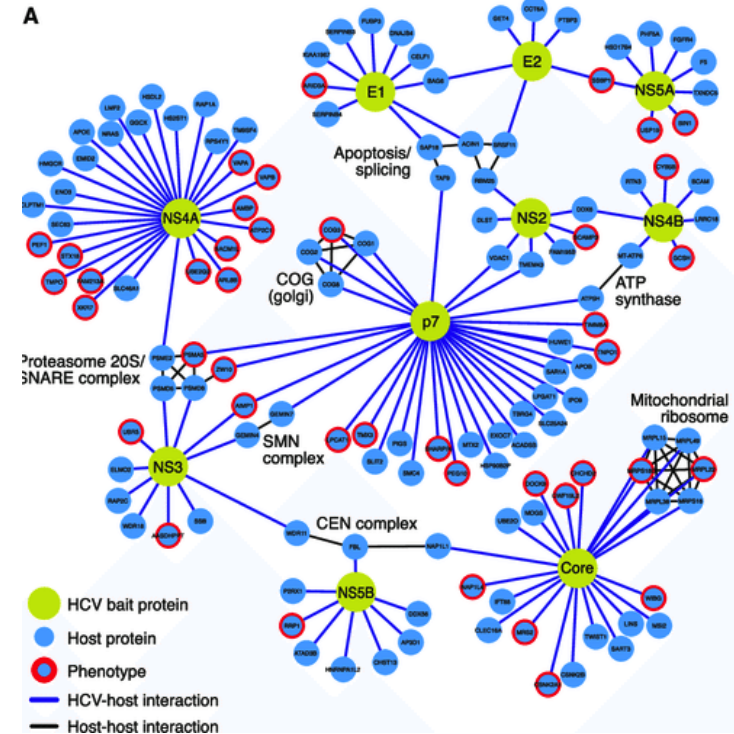
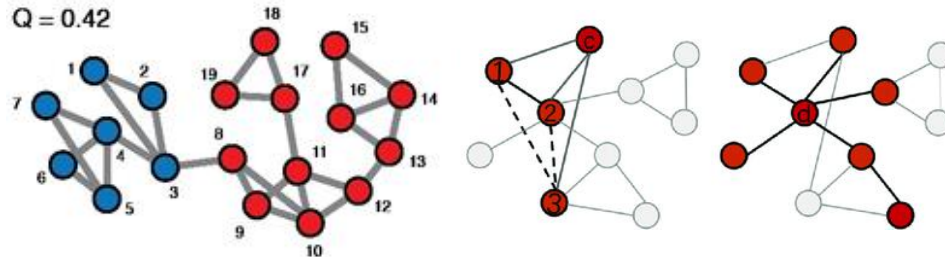


E) Replication Timing



Biological networks

- Topological properties of networks
 - Relationship to biology
- Applications in biomedicine
- Visualization and analysis with Cytoscape



Source: Ramage et al. Mol Cell (2015)

Module 5: Python skills



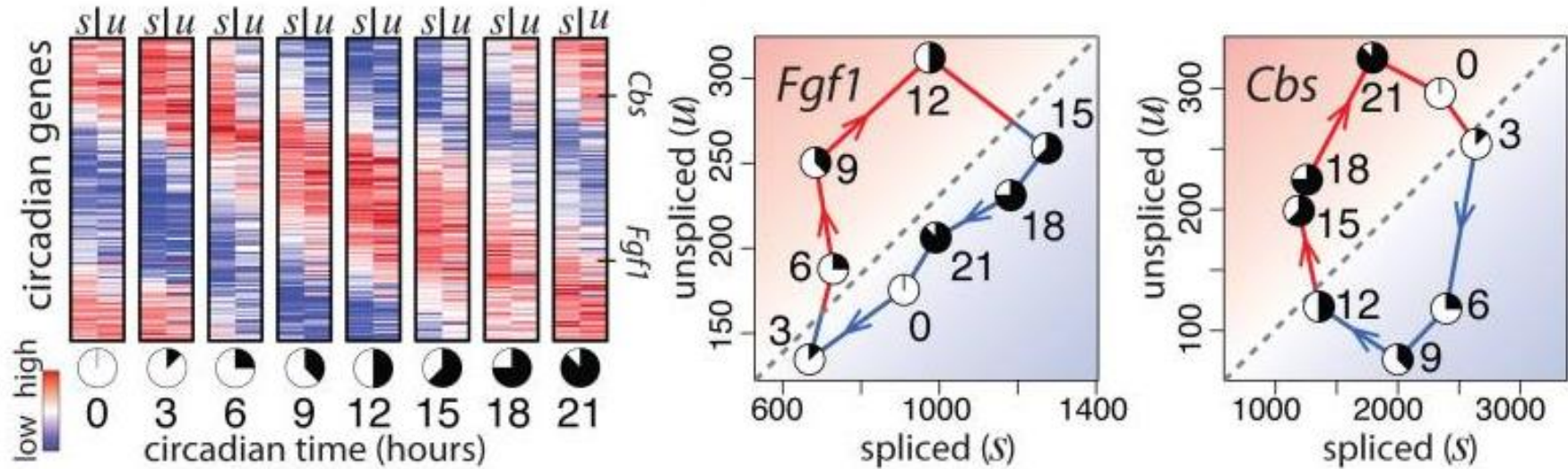
- Kaggle's programming courses
- In-class practice & problem sets
 - Handling of tabular data
 - Statistical analyses
 - Visualizations
- We will spend 8 sessions on top of Kaggle's courses to get a solid foundation

Module 6: Machine learning



- Unsupervised learning
 - PCA, PCoA, t-SNE, UMAP
 - Clustering techniques
- Supervised learning
 - Predict cancer subtype
 - Identify potential biomarker genes
- (a touch of) Deep learning
 - AlphaFold

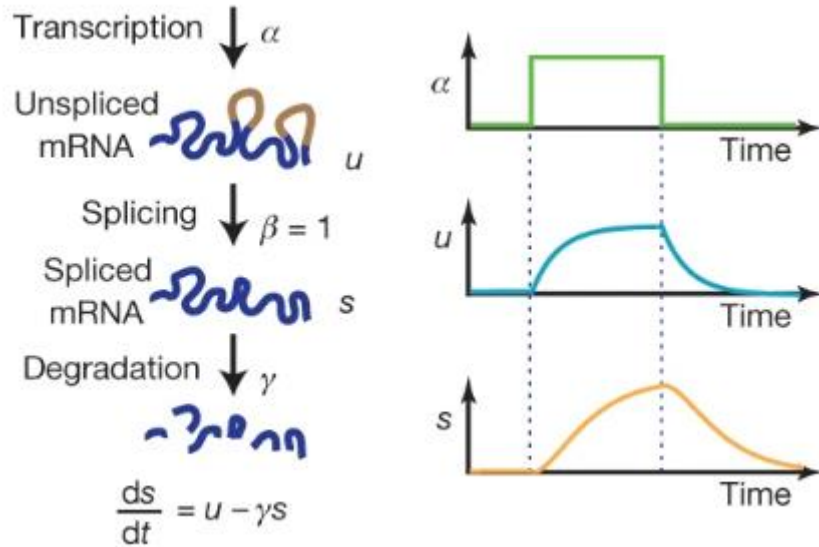
A taste of dynamics modeling in Systems Biology



La Manno et al. Nature 2018

- Gene upregulation first produce unspliced RNA
- Followed by processing into mature RNA and proteins

RNA velocity model



La Manno *et al.* Nature 2018

- Model RNA synthesis as differential equations
- Simulation can be performed to analyze the dynamics of the system
 - Try various parameter values

Any questions?



See you next week on August 21st