Modeling cancer cells using multi-comics data

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The Second Korea-Japan Machine Learning Workshop

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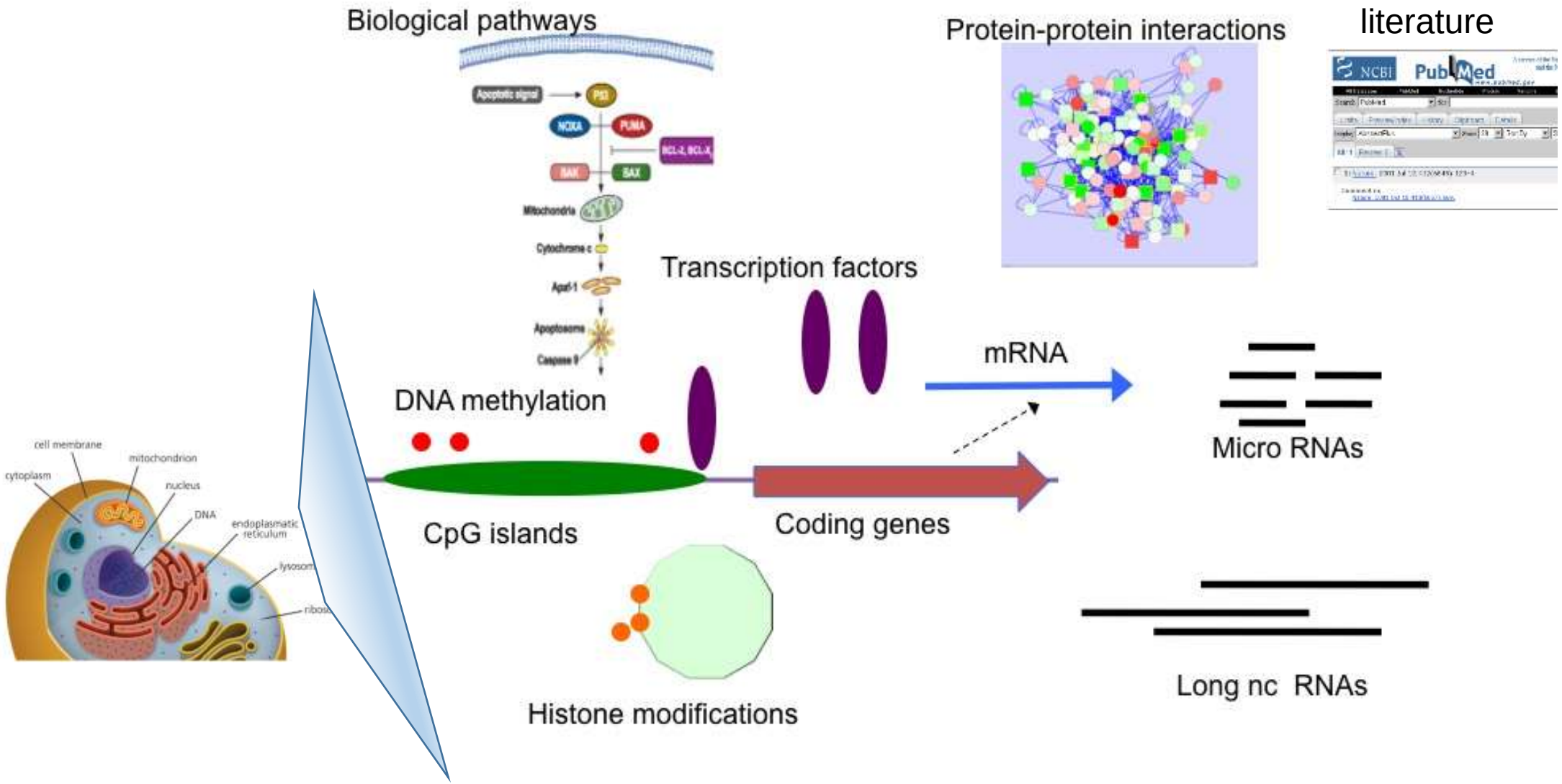
Cells, Genetic and Epigenetic Elements



Our Strategies

- **Understanding biological sequences**
- **Capturing a bigger picture**
- **Modeling complex relationships**
- **Multi-omics data integration**
- **Driver gene identification**
- **Dynamics from time-series data analysis**

Today

I will present three of the recently submitted (unpublished) manuscripts towards this goal.

(1) sequence level: *Ranked k-spectrum kernel for comparative and evolutionary comparison of exons, introns, and CpG islands*

(2) transcript level: *Cancer subtype classification and modeling by pathway attention and propagation,* (**poster by Sangseon Lee**) and

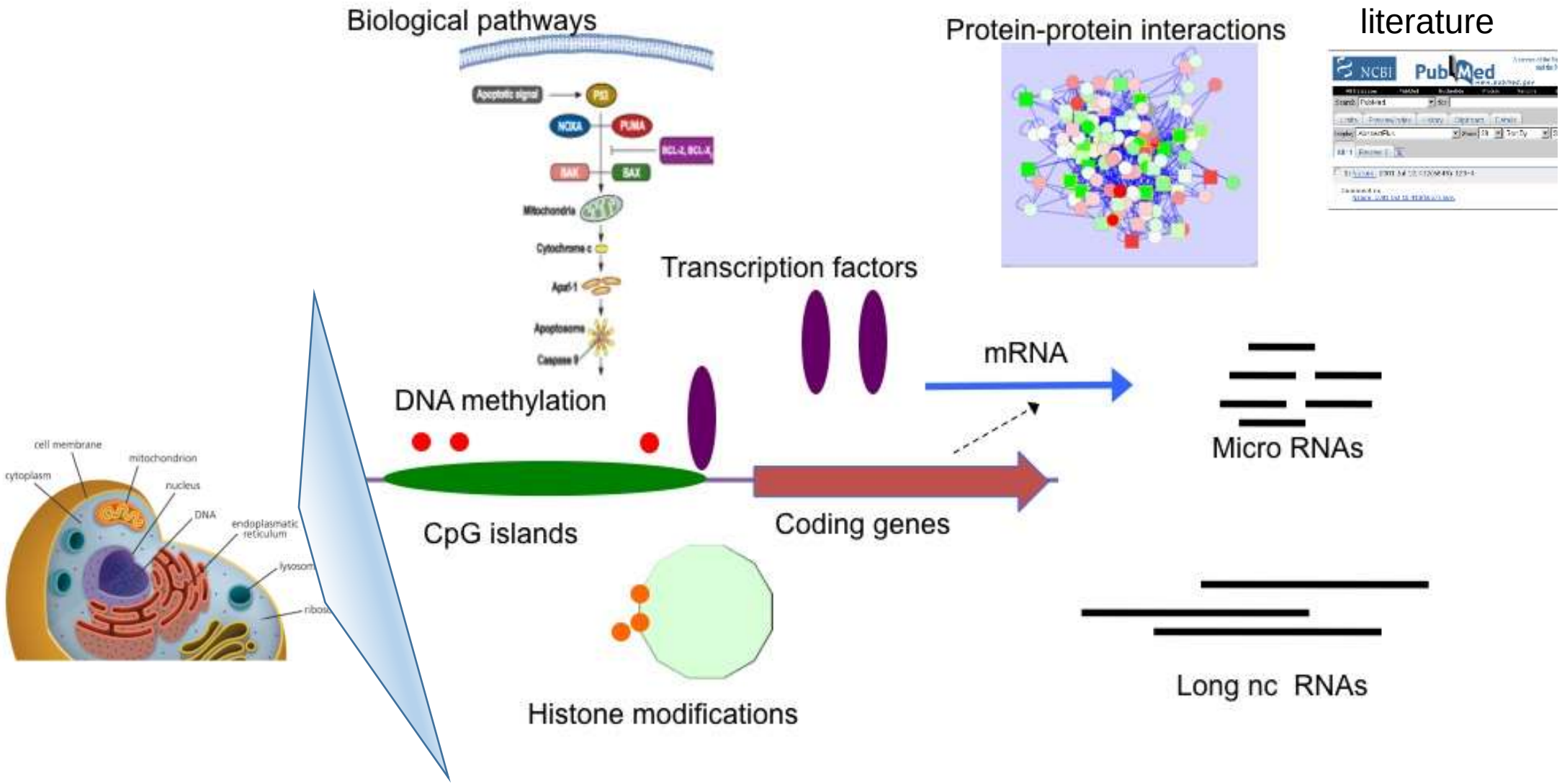
(3) epigenetic level: *PRISM: Methylation Pattern-based, Reference-free Inference of Subclonal Makeup.* (**poster by Dohoon Lee**)

Ranked k-spectrum kernel for comparative and evolutionary comparison of exons, introns, and CpG islands

Sangseon Lee, Taeheon Lee, Yung-Kyun Noh, and Sun Kim

Bio & Health Informatics Lab.

Cells, Genetic and Epigenetic Elements



Biological sequence analysis

- The heart of bioinformatics research
  - Alignment of biological sequences
  - Phylogeny
  - Gene prediction
  - Structure prediction

Two type of methods for biological sequence analysis

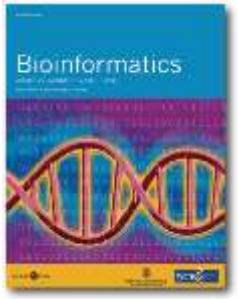
- Alignment-based method
  - Smith-Waterman or BLAST
  - Successfully used due to accuracy
  - Cost expensive
  - Hard to handle high throughput sequencing data due to variable length and amounts of sequences

- Alignment-free method
  - Based on k-mer frequency vectors
  - Measure distance between two vectors by Euclidean distance or Kullback-Leibler discrepancy.

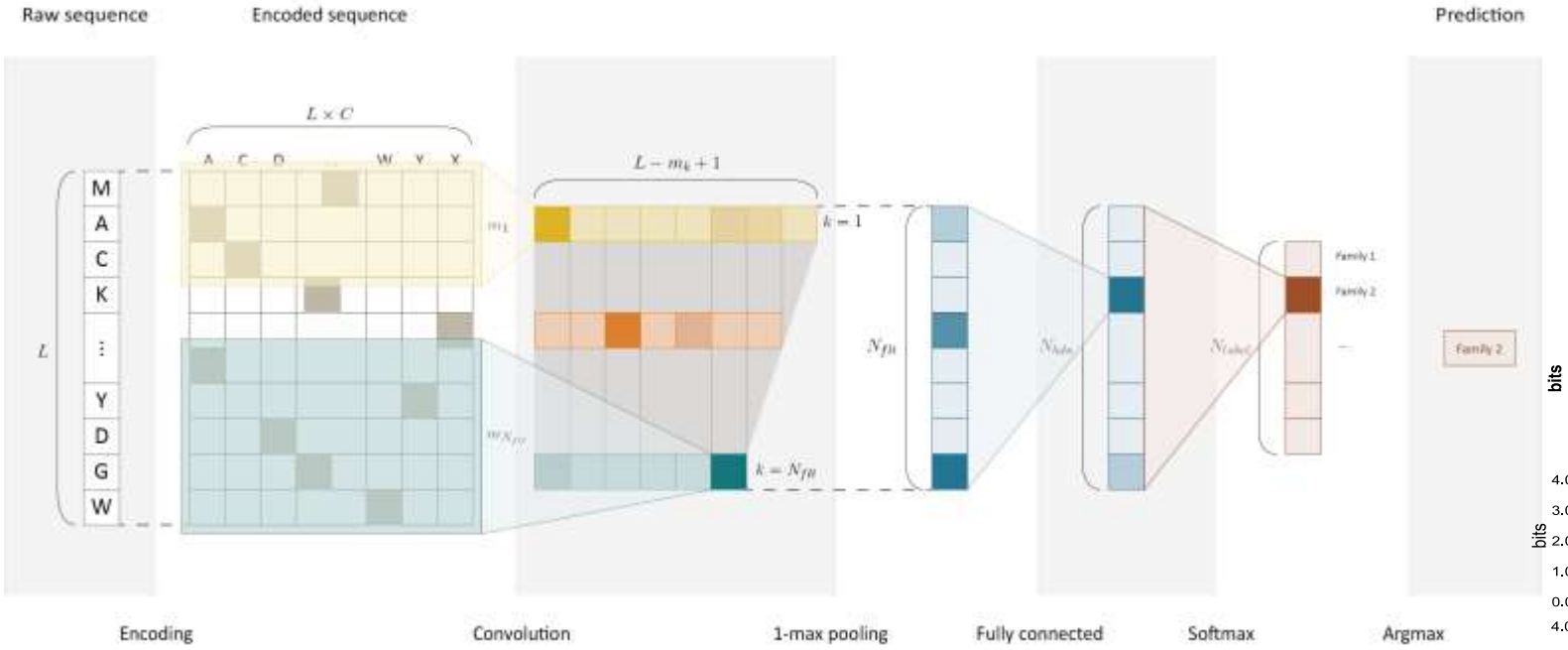
  → String kernel method

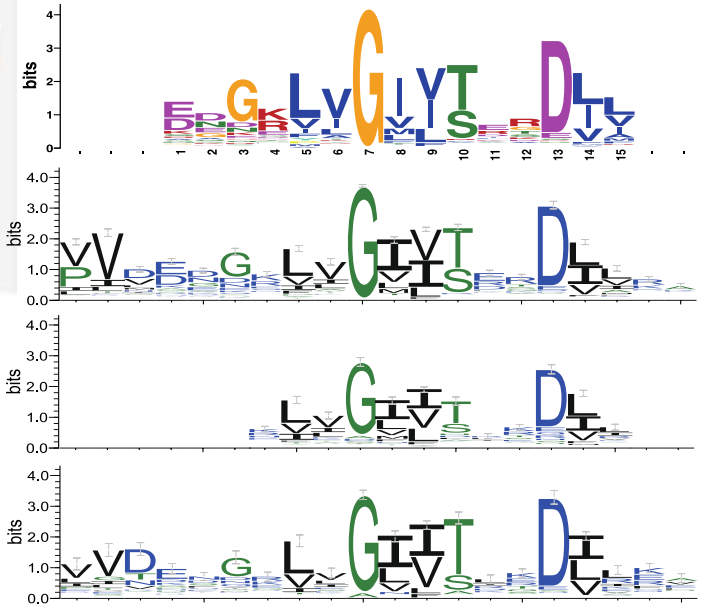
K-mer based Alignment-free Sequence Analysis

- Among others, two major issues:
  - Length of k-mer
  - Comparison of genome scale sequences



DeepFam: Deep learning based alignment-free method for protein family modeling and prediction (ISMB 2018)





String kernel method for comparative and evolutionary sequence comparison

- Traditional String kernel method: k-spectrum kernel (Leslie, 2006)
  - Designed for protein sequence classification
  - Various expansions: mismatch, various k-length, and so on
  - **Limited for comparative and evolutionary comparison of multiple species**
    - Pairwise distance of two genomes → combine many pairwise distances is not straightforward
    - k-spectrum kernel is sensitive to over-represented k-mers
- Propose New string kernel method: *Ranked K-spectrum string (RKSS) kernel*

K-spectrum string kernel

- On the input space $\mathcal{X}$ of all finite length sequences of characters from alphabet $\mathcal{A}$, $|\mathcal{A}| = l$ ($l = 4$ for DNA), a feature map from $\mathcal{X}$ to $\mathbb{R}^{l^k}$,

$$\Phi_k(x) = \left(\phi_\alpha(x)\right)_{\alpha \in \mathcal{A}^k}$$

$\phi_\alpha(x)$: the number of times α occurs in x

- K-spectrum string kernel

$$K_k(x, y) = \langle \Phi_k(x), \Phi_k(y) \rangle$$

- Kernel distance

$$\widetilde{K}_k(x, y) = \frac{K_k(x, y)}{\sqrt{K_k(x, x)}\sqrt{K_k(y, y)}}$$

$$D_k(x, y) = \sqrt{\widetilde{K}_k(x, x) + \widetilde{K}_k(y, y) - 2\widetilde{K}_k(x, y)}$$

Ranked k-spectrum string (RKSS) kernel

- Two main features of RKSS kernel
  - Build and use **common** k-mers template (= **landmark**) to encapsulate information of common ancestry
  - Use of correlation in rank of k-mers instead of occurrence counts

- RKSS kernel

$$K_k^{Rank}(x,y) = RC(\Phi_k^{common}(x), \Phi_k^{common}(y))$$

RC: the Kendall tau rank correlation
Φ_k^{common}: a feature map on the landmark

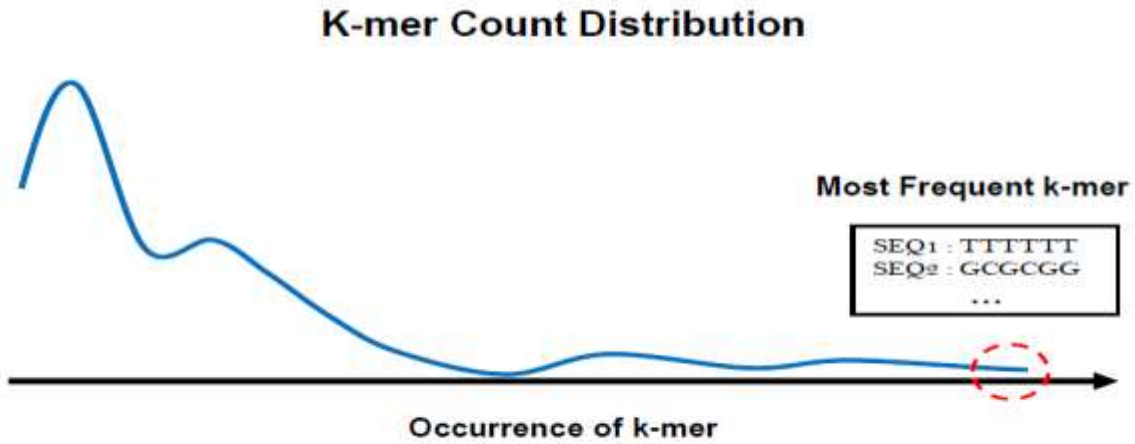
- Kernel distance

$$\widetilde{K}_k^{Rank}(x,y) = \frac{1 + K_k^{Rank}(x,y)}{2}$$

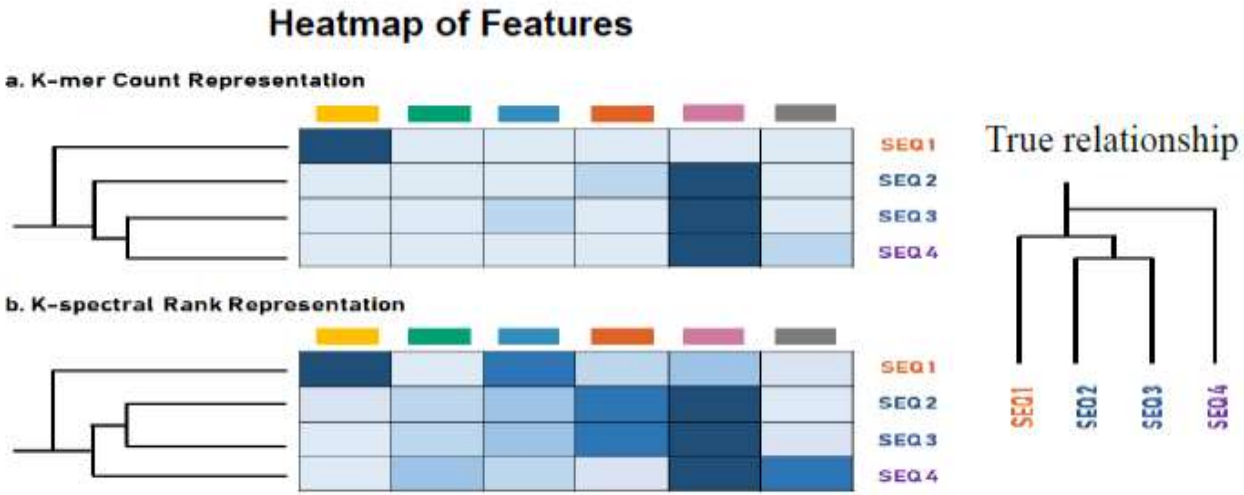
$$dist(x,y) = \sqrt{\widetilde{K}_k^{Rank}(x,x) + \widetilde{K}_k^{Rank}(y,y) - 2\widetilde{K}_k^{Rank}(x,y)}$$

$$= \sqrt{1 - \widetilde{K}_k^{Rank}(x,y)}$$

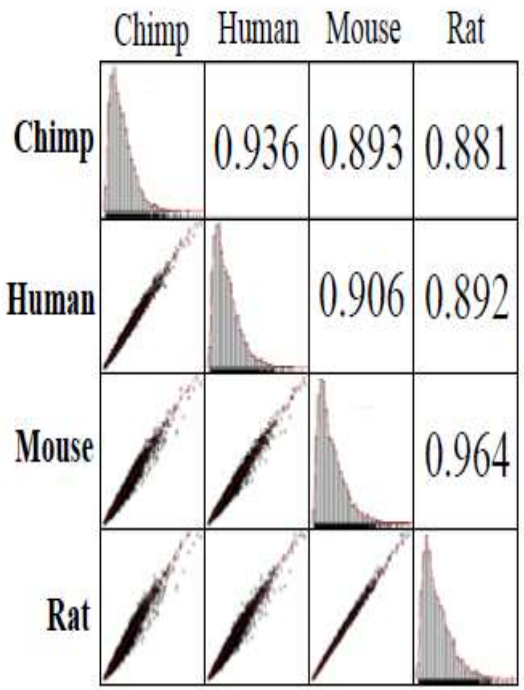
Effect of rank information



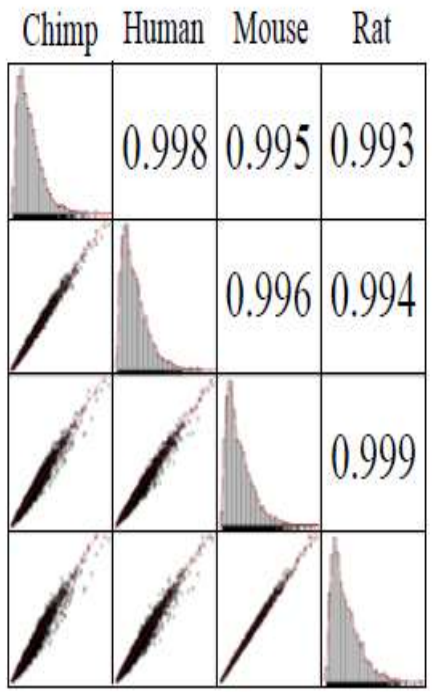
(a) Long tail distribution of k-mer frequency



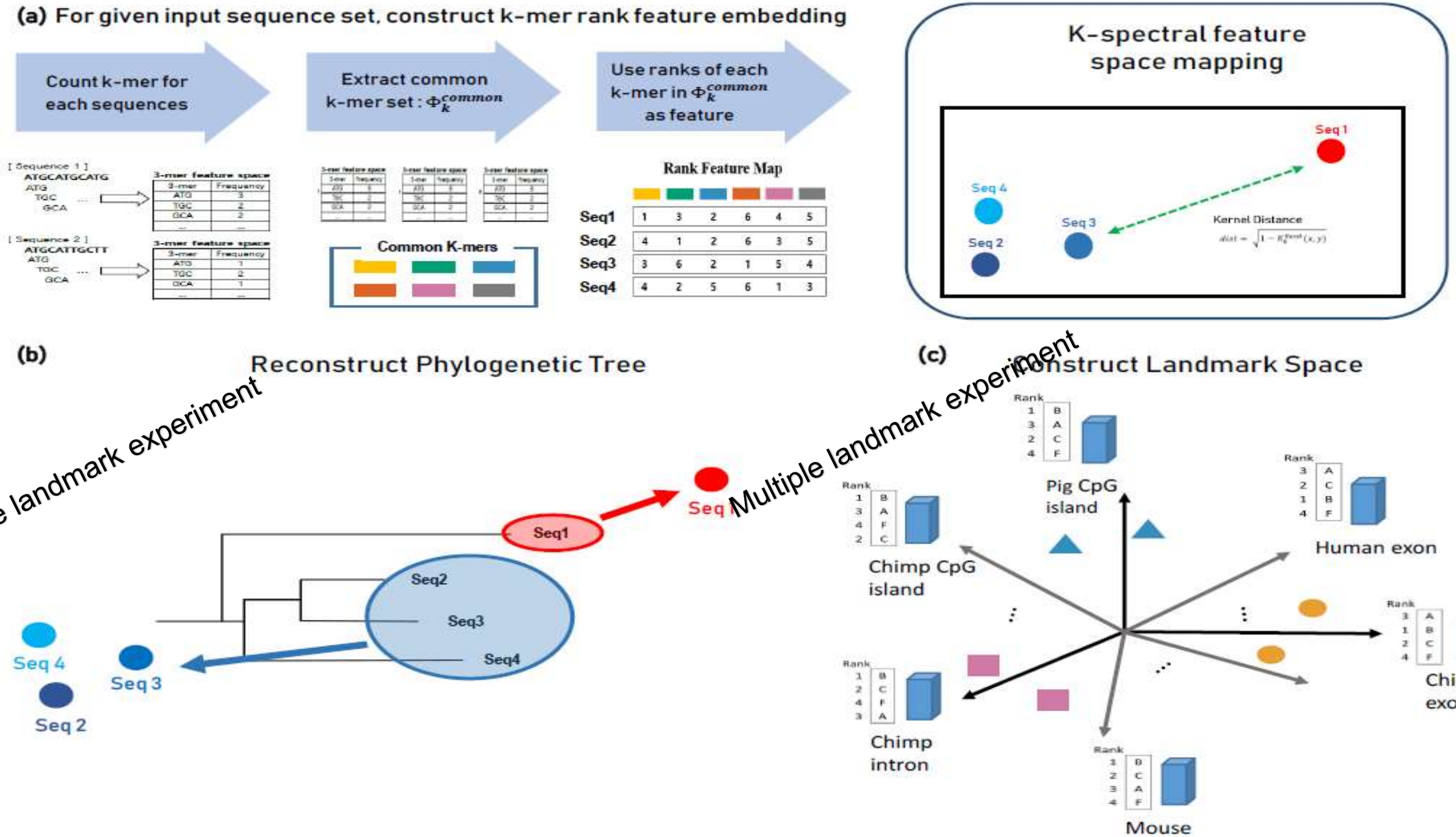
(b) Effect of rank information



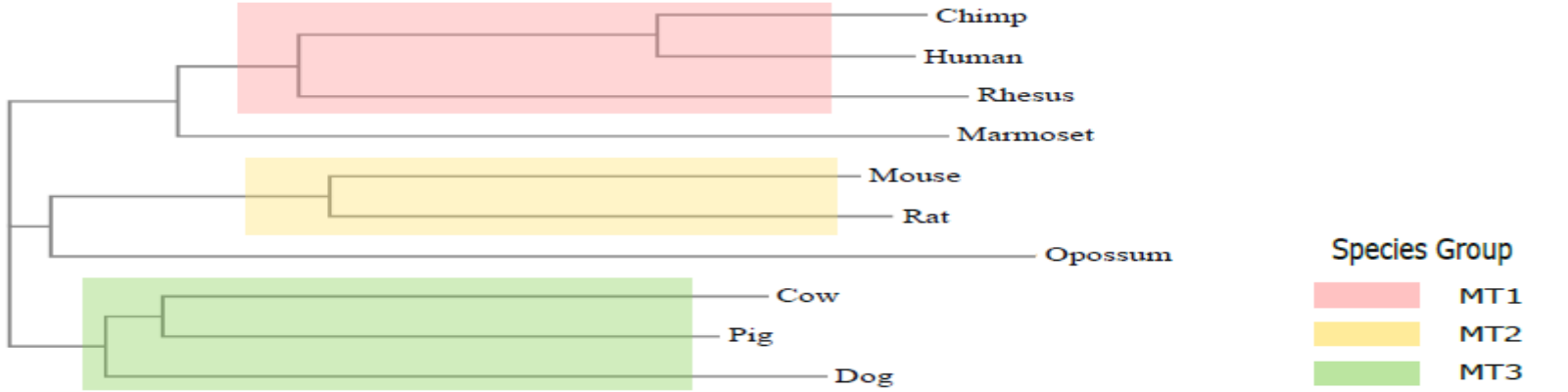
(a) Similarity by RKSS kernel



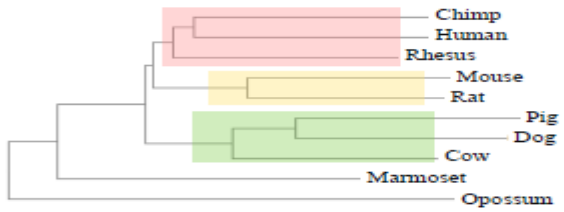
(b) Similarity by Spectrum kernel


(a) For given input sequence set, construct k-mer rank feature embedding
Count k-mer for each sequences
Extract common k-mer set : Φ_k^{common}
Use ranks of each k-mer in Φ_k^{common} as feature
[Sequence 1]
ATGCATGCATG
ATG
TGC
GCA
[Sequence 2]
ATGCATTGCTT
ATG
TGC
GCA
3-mer feature space
3-mer
Frequency
Common K-mers
Rank Feature Map
Seq1 1 3 2 6 4 5
Seq2 4 1 2 6 3 5
Seq3 3 6 2 1 5 4
Seq4 4 2 5 6 1 3
K-spectral feature space mapping
Seq 1
Seq 2
Seq 3
Seq 4
Kernel Distance
(b)
Reconstruct Phylogenetic Tree
Single landmark experiment
Seq1
Seq2
Seq3
Seq4
Seq 4
Seq 3
Seq 2
(c)
Reconstruct Landmark Space
Multiple landmark experiment
Rank
Pig CpG island
Chimp CpG island
Human exon
Chimp exon
Chimp intron
Mouse

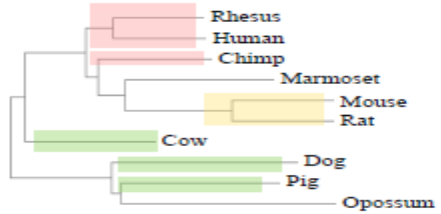
Phylogenetic tree reconstruction on exon, intron, and CpG island



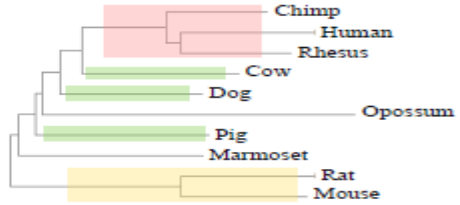
(a) The mitochondria tree



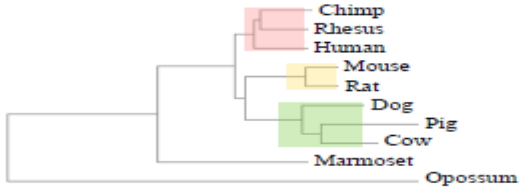
(b) The exon tree of RKSS kernel



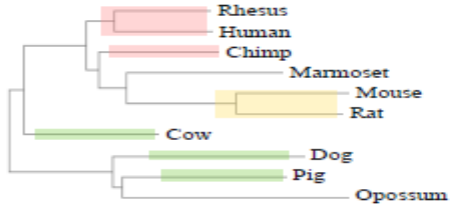
(c) The CpG island tree of RKSS kernel



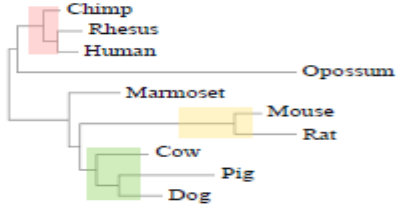
(d) The intron tree of RKSS kernel



(e) The exon tree of spectrum kernel



(f) The CpG island tree of spectrum kernel

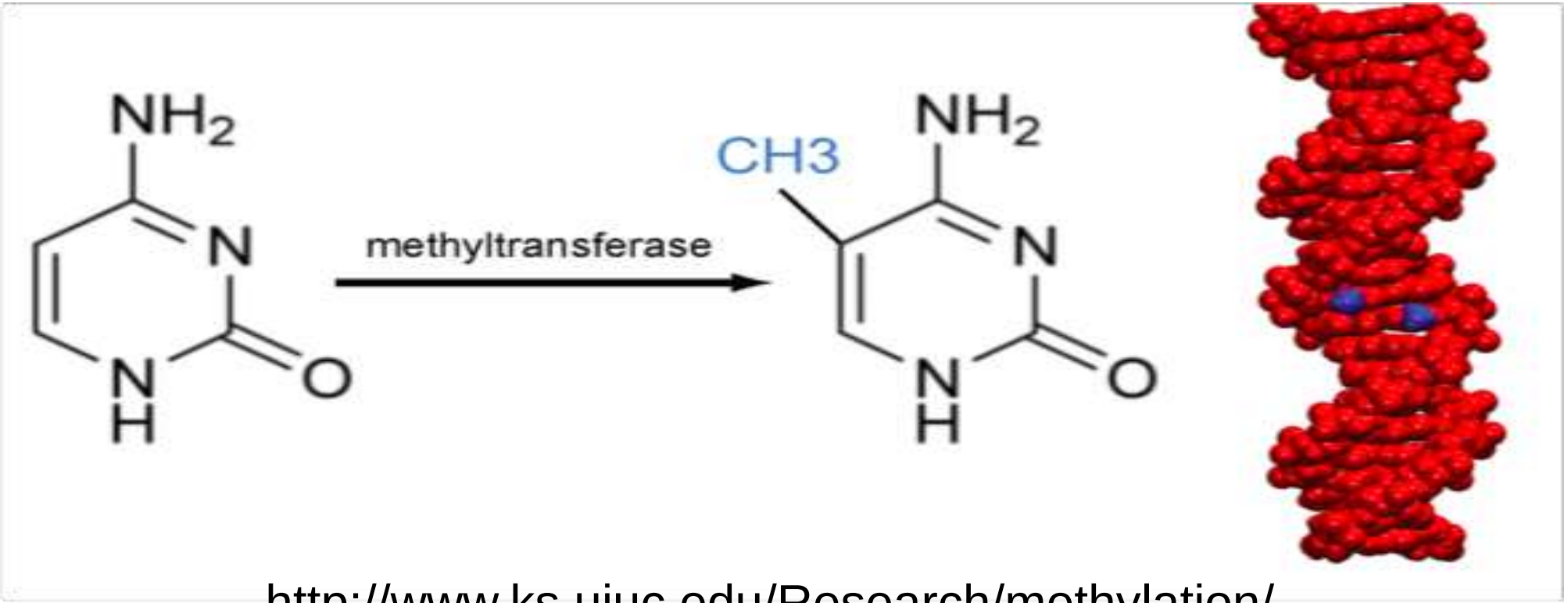


(g) The intron tree of spectrum kernel

Human CpG Island Sequences

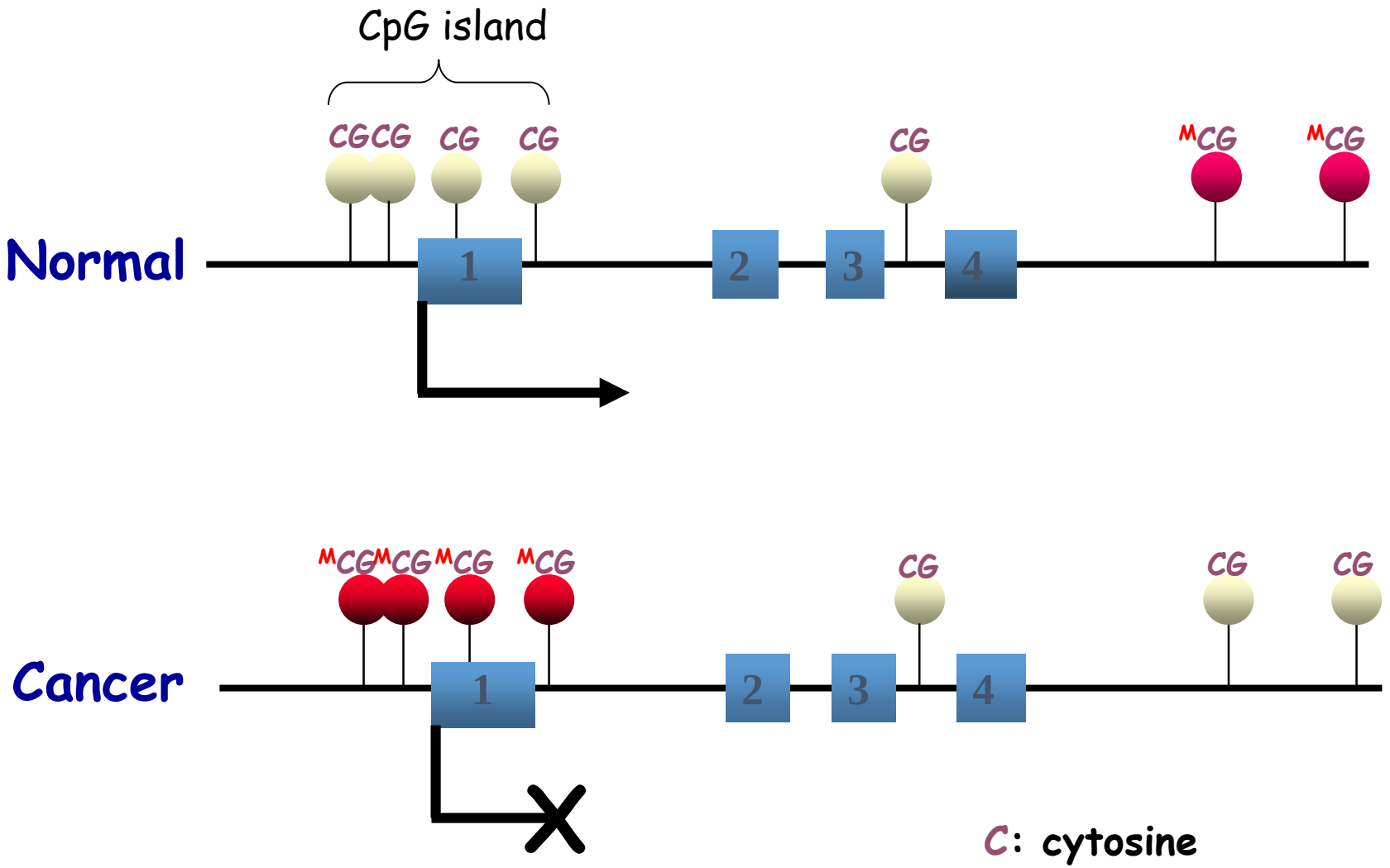
```
>chr1_788863_789211_CpG: 28
TGGTAAACTGATGAACCCCGACCCTGATGAACGTGAGATGACCGCCGTGTGGTAAACTGATGAACCCCGACC
CGTGAGATGACCGCCGTGTGGTAAACTGATGAACCCCGACCCTGATGAACGTGAGATGACCGCCGTGTGGTA
AACCCCGACCCTGATGAACGTGAGATGACCGCCGTGTGGTAAACTGATGAACCCCGACCCTGATCAACGTGA
CCGTGTGGTAAACTGATGAACCCCGACCCTGATGAACATGAGATGACCGCCGTGTGGTAAACTGATGAACCC
ATCAACATGAGATGACCGCCG
>chr1_801975_802338_CpG: 24
CCGTGCCCTCACGTGGTCCTCCCTCTGCACTCACATCCCTGACGTCCTCCCGTGCCCTCACGTGGTCCTCCC
CACATCCCTGACGTCCTCCCGAGCCCTCACGTGGTCCTCCCTCTGCACTCACATCCCTGACGTCCTCCCGTG
TGGTCCTCCCCCTGCACTCACATCCCTGACGTCCTCCCGAGCCCTCACGTGGTCCTCCCCCTGCACTCACAT
TCCTCCCGAGCCCTCACGTGGTCCTCCCCCTGCACTCACATCCCTGACGTCCTCCCGAGCCCTCACGTGGTC
GCACTCACATCCCTGACGTCCTCCCGAGCCCTCACG
>chr1_805198_805628_CpG: 50
CTGGGCCACGCCCACTCCCCCACGCGGGGAAGGAGCTTCGCGCTGCCGCCTGGCTGGGGACTGGGCACGCCC
CTCCGGAGCCGGCTGCCACCAGGGGGCGCGCCCGCGGTGTCCGGGAGCCTGGCGGCGCCTGTGCAGCGGCCA
GCTCCTGCCCTCGCCTCGGTCTCTGCCAGGACCCCGACGCCCAGCCGGACCCTGCCCTCCAGCGGGGCCGCG
GCCCGCAACAGCAGCCCCACCCGGCATTCGGCGCGCTCCGCGGGGCAGAGGTCGCGGTGTCCTCAGGCTGTG
CTACAACCCCCACGCCGGGCCCGGGCCCCGTGATTATATTTGGGCCCCGTGTGATTATATTTGACAGGTCTT
CGCTGTTCAGCGCTTTGAGTTCG
```

DNA Methylation

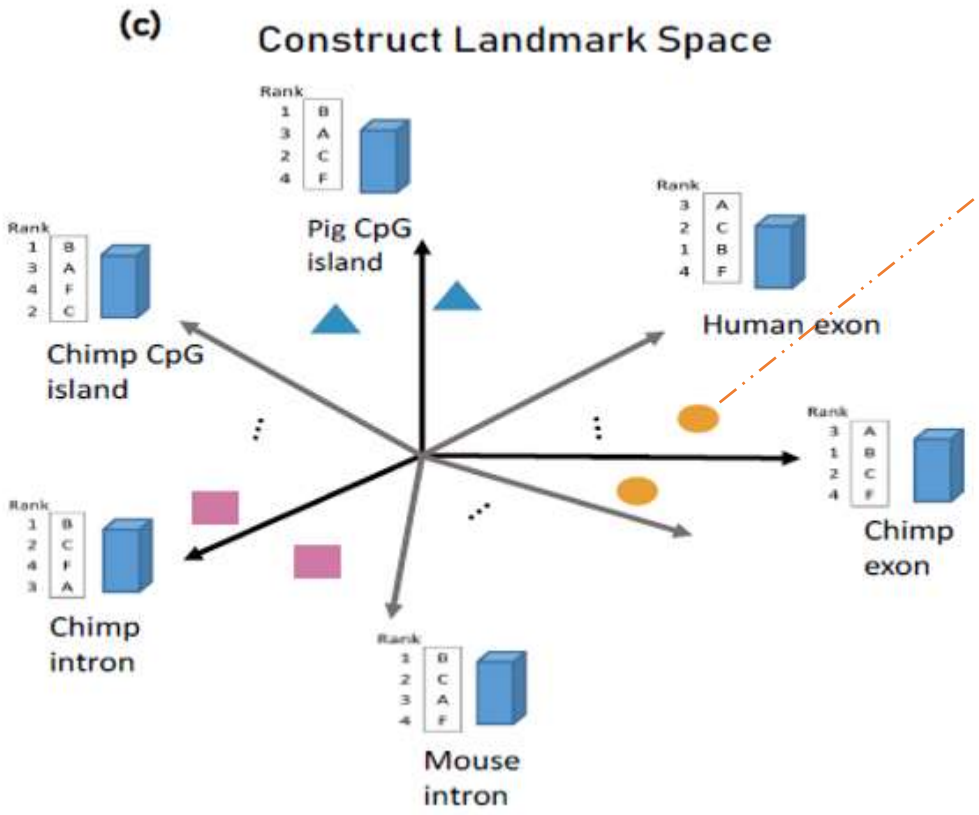


http://www.ks.uiuc.edu/Research/methylation/

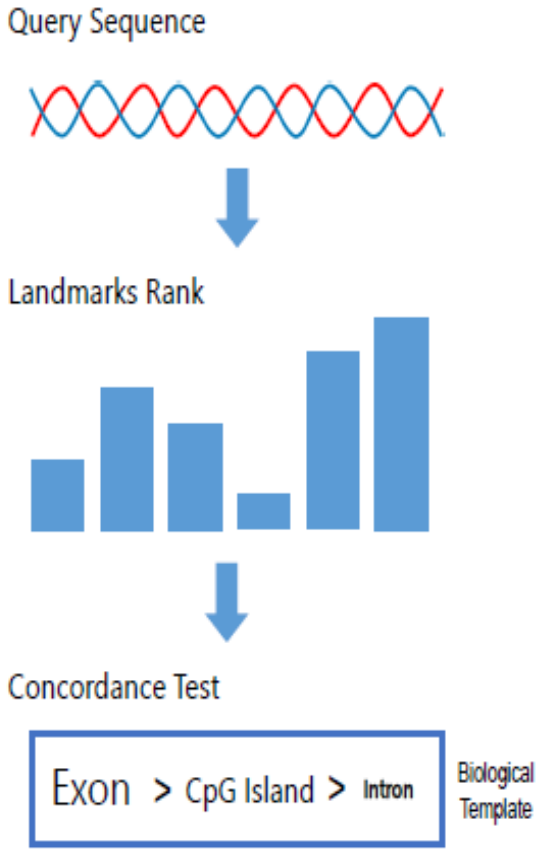
DNA Methylation and Gene Silencing in Cancer Cells



Measure Information contents on genomic regions using Landmark space



Pipeline of concordance test



Example of processing algorithm

Distances to Landmarks

Cow Exon	Cow CpGI	Cow Intron	Rat Exon	Rat CpGI	Rat Intron
0.31	0.53	0.86	0.37	0.56	1.23

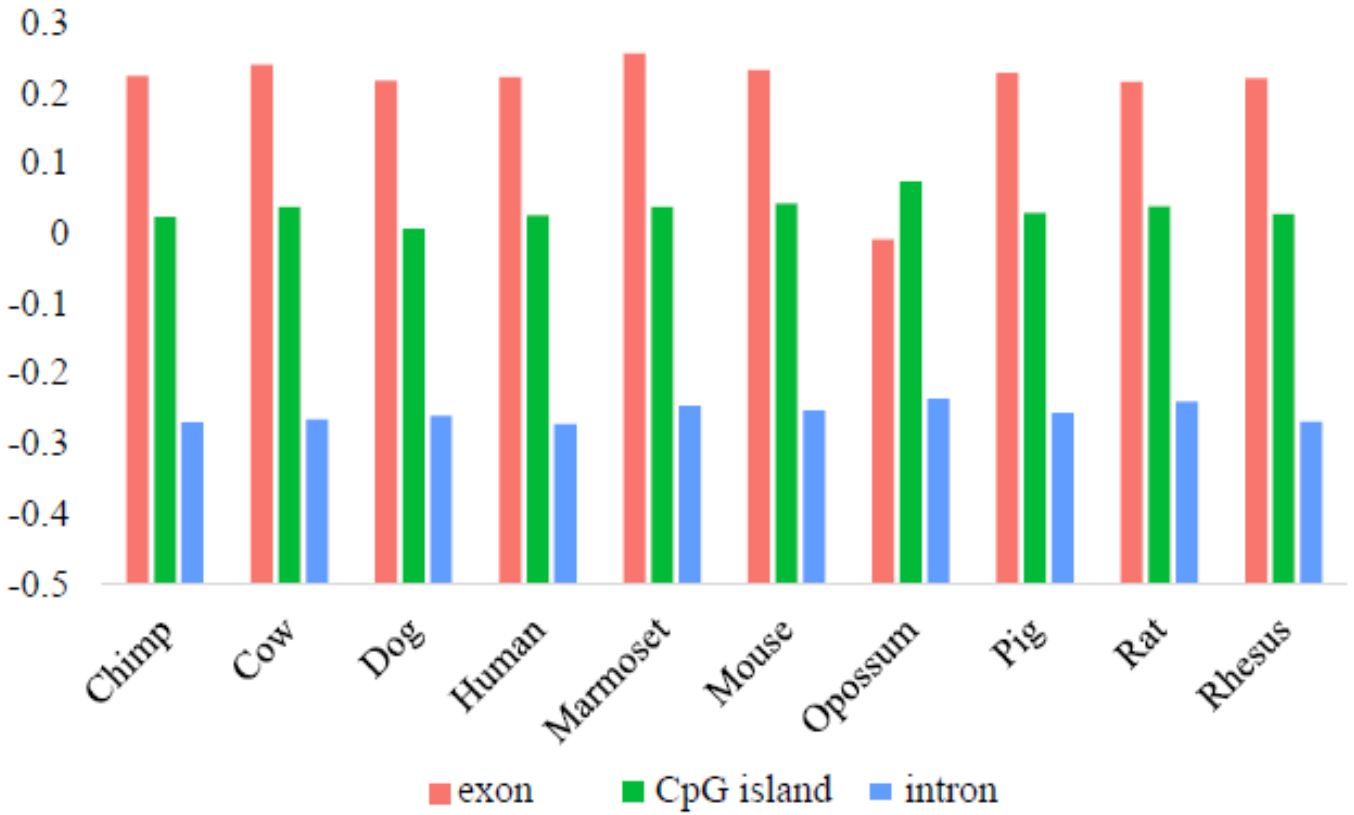
Cow Exon	Cow CpGI	Cow Intron	Rat Exon	Rat CpGI	Rat Intron
1	3	5	2	4	6

Information theoretic concordance test on rank

Rank Template

Cow Exon	Cow CpGI	Cow Intron	Rat Exon	Rat CpGI	Rat Intron
1	2	3	1	2	3

Measure Information contents on genomic regions using Landmark space



Conclusion

- Using landmark and rank information of k-mers, we proposed new string kernel method for comparative and evolutionary sequence comparison.
  - Ranked k-mer spectrum string (RKSS) kernel
- From two landmark-based experiments,
  - We demonstrated effectiveness of RKSS kernel on phylogeny reconstruction problem.
  - In addition, we found the relationship across the information contents in exons, introns, and CpG islands.
  - In terms of evolutionary information, the order of three region was like that:
    exon > CpG island > intron.

Cancer subtype classification and modeling by pathway attention and propagation

Sangseon Lee, Sangsoo Lim, Taeheon Lee, and Sun Kim

Pathway: A prior knowledge for Bioinformatics Analysis

- A graph-based representation of biological system

Enrichment Test

Enrichr: a comprehensive gene set enrichment analysis web server 2016 update

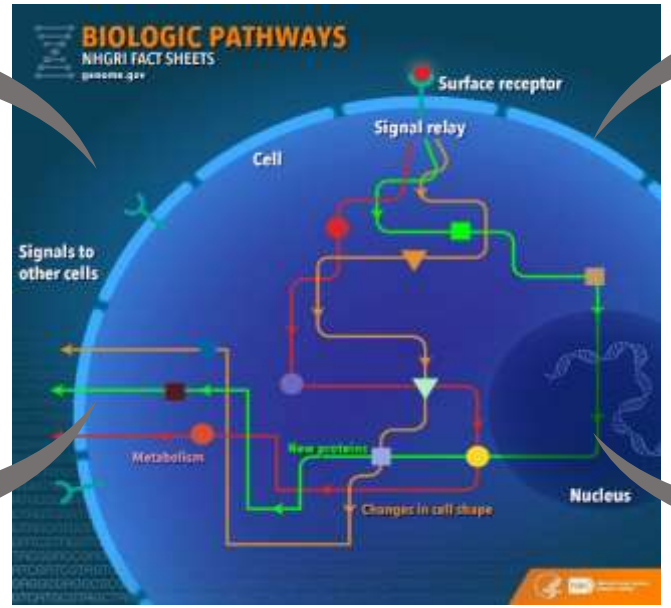
Maxim V. Kuleshov[1], Matthew R. Jones[1], Andrew D. Rouillard[1], Nicolas F. Fernandez[1], Qiaonan Duan[1], Zichen Wang[1], Simon Koplev[1], Sherry L. Jenkins[1], Kathleen M. Jagodnik[2], Alexander Lachmann[1], Michael G. McDermott[1], Caroline D. Monteiro[1], Gregory W. Gundersen[1] and Avi Ma'ayan[1,*]

Pathway Activity Inference

BIOINFORMATICS

Inference of patient-specific pathway activities from multi-dimensional cancer genomics data using PARADIGM

Charles J. Vaske[1,†], Stephen C. Benz[2,†], J. Zachary Sanborn[2], Dent Earl[2], Christopher Szeto[2], Jingchun Zhu[2], David Haussler[1,2] and Joshua M. Stuart[2,*]



Dimension Reduction

Comprehensive and critical evaluation of individualized pathway activity measurement tools on pan-cancer data

Sangsoo Lim, Sangseon Lee, Inuk Jung, Sungmin Rhee and Sun Kim

Subpath Mining

Methods

MIDAS: Mining differentially activated subpaths of KEGG pathways from multi-class RNA-seq data

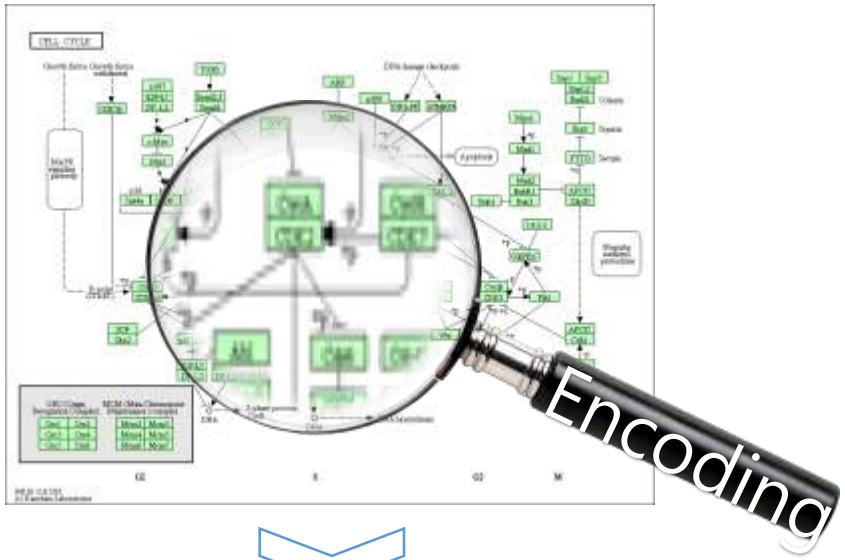
Sangseon Lee[a], Youngjune Park[b], Sun Kim[a,b,c,*]

Cancer subtype classification and modeling by pathway attention and propagation

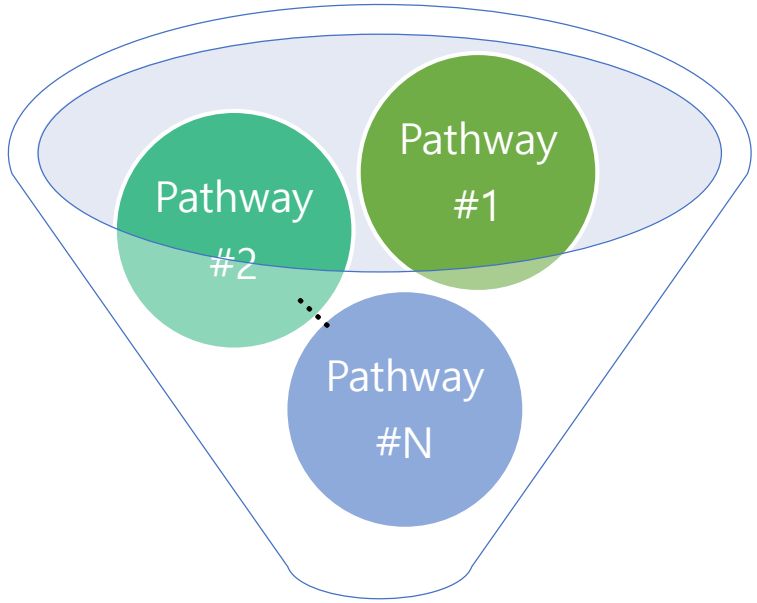
- What to do:
  - To model mechanisms of cancer subtypes in terms of biological pathways,
- How to do this:
  - *Graph convolutional network* (GCN) modeling of each biological pathway
  - Integration of 287 GCNs using *attention mechanisms*.
  - To open up the black-box the GCN ensemble model, we used *graph propagation* technique to explain how pathway interact differently in cancer subtypes

Two major points of modeling cancer subtypes with pathways

RNA-seq



Useful Information

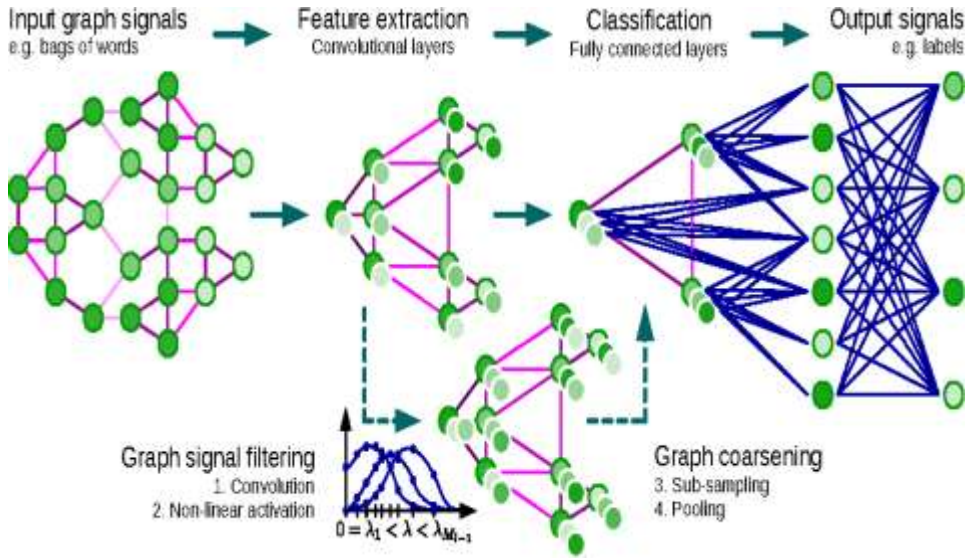


A Comprehensive Biological Mechanism

Idea to address two challenges

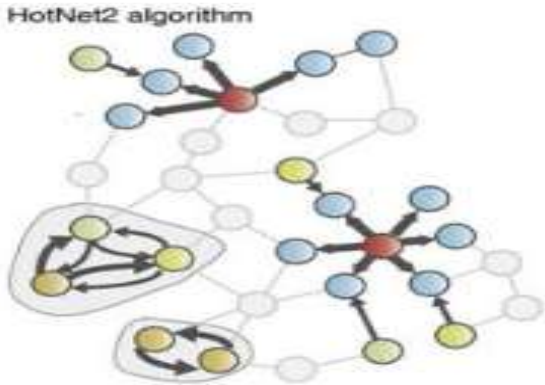
Encoding Pathway Information

- Graph Convolutional Network (GCN)



Pathway Aggregation with interactions

- Open “black-box” using *attention*
  - Merge pathways by MLP, i.e. Fully Connected Layers
  - It is hard to interpret. “BLACK-BOX”
  - Solution: Attention!!
- Consider pathway interactions by *Network propagation*



What & How to Achieve

Goal

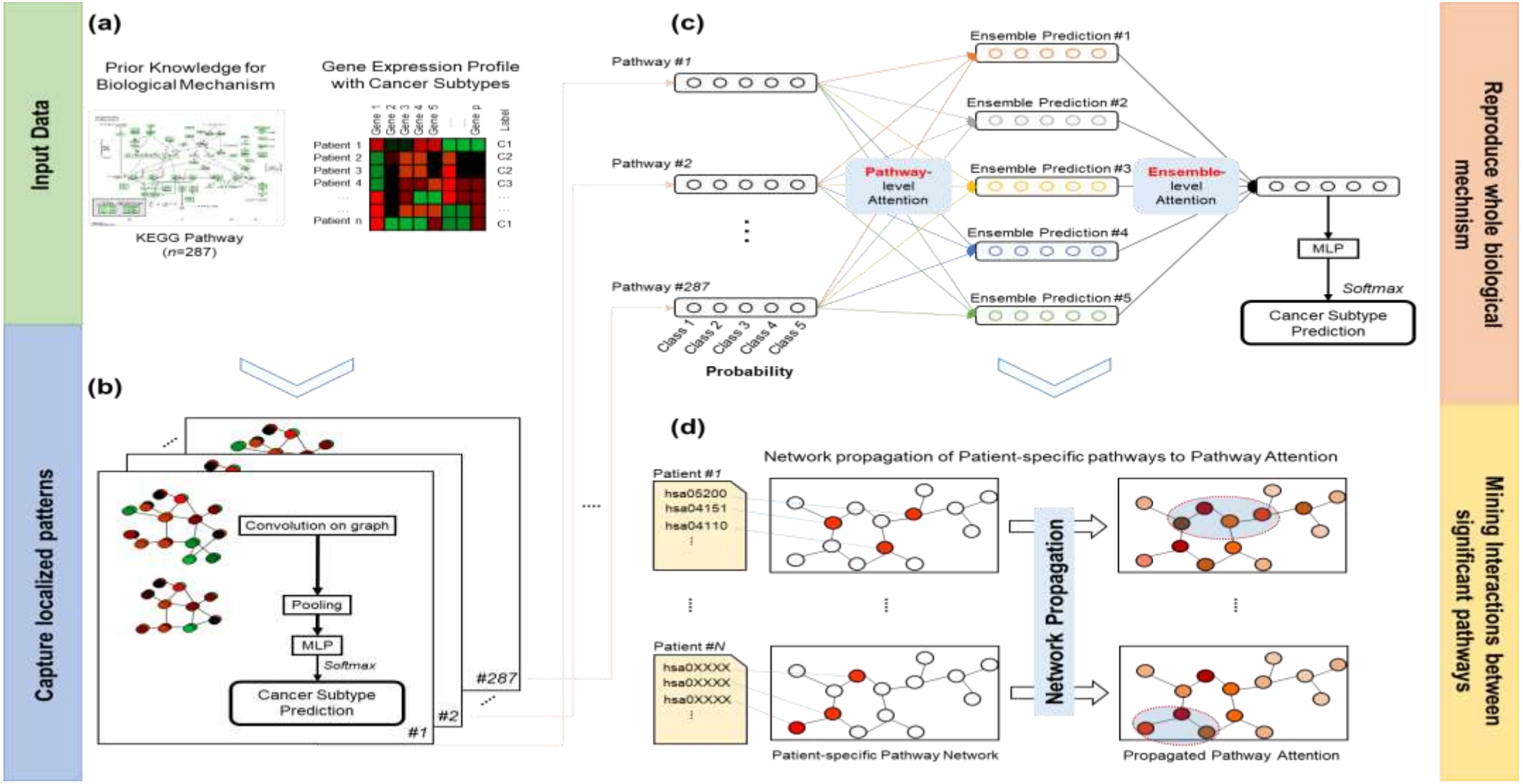
- Modeling cancer subtypes with considering
  - comprehensive biological mechanism
  - Interaction between pathways

Input & Output

- Input
  - Gene expression profile with cancer subtype
  - Biological pathways
- Output
  - Classification of cancer subtypes
  - Importance of pathways with interaction information

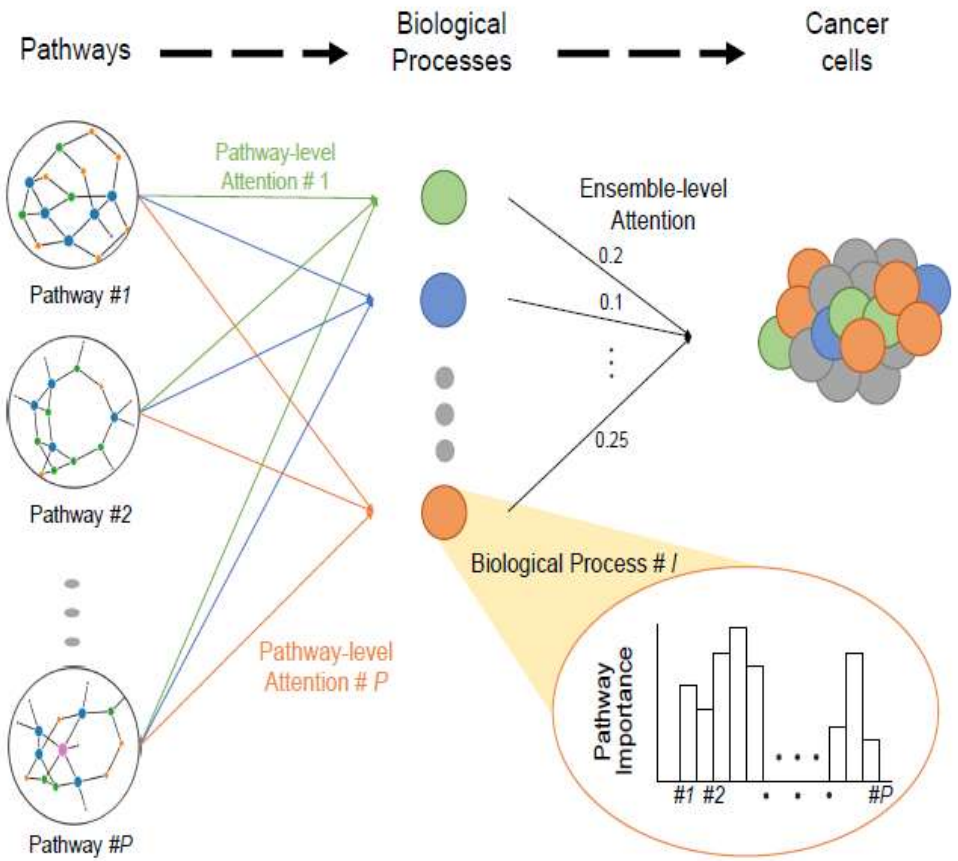
    ← Attention & Networkpropagation

Workflow

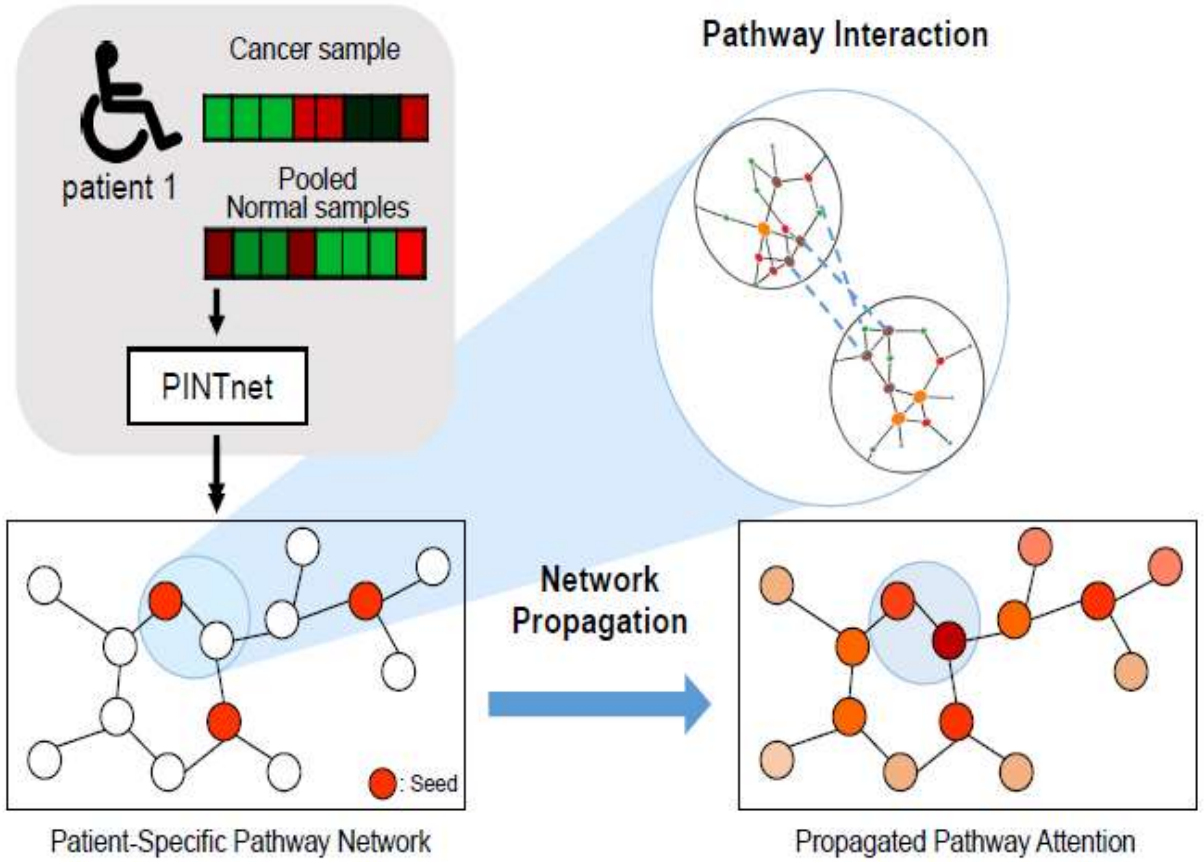

Input Data
Capture localized patterns
Reproduce whole biological mechnism
Mining Interactions between significant pathways
(a)
Prior Knowledge for Biological Mechanism
KEGG Pathway (n=287)
Gene Expression Profile with Cancer Subtypes
Gene 1
Gene 2
Gene 3
Gene 4
Gene 5
Gene p
Label
Patient 1
Patient 2
Patient 3
Patient 4
Patient n
C1
C2
C2
C3
C1
(b)
Convolution on graph
Pooling
MLP
Softmax
Cancer Subtype Prediction
#1
#2
#287
(c)
Pathway #1
Pathway #2
Pathway #287
Pathway-level Attention
Ensemble Prediction #1
Ensemble Prediction #2
Ensemble Prediction #3
Ensemble Prediction #4
Ensemble Prediction #5
Ensemble-level Attention
MLP
Softmax
Cancer Subtype Prediction
Class 1
Class 2
Class 3
Class 4
Class 5
Probability
(d)
Network propagation of Patient-specific pathways to Pathway Attention
Patient #1
hsa05200
hsa04151
hsa04110
Patient #N
hsa0XXXX
hsa0XXXX
hsa0XXXX
Network Propagation
Patient-specific Pathway Network
Propagated Pathway Attention

Biological Interpretation of *Attention* and *Network propagation*

Multi attention based ensemble (MAE)



Network propagation on patient-specific pathway network



Dataset

Cancer	Total	Subtypes	Source
BLCA	408	Basal_squamous (142), Luminal (26), Luminal_infiltrated (78), Luminal_papillary (142), Neuronal	*
BRCA	1097	Basal (230), Her2 (161), LumA (318), LumB (298), Normal-like (90)	**
COAD	245	CMS1 (39), CMS2 (78), CMS3 (37), CMS4 (68), NOLBL (23)	*
PRAD	317	ERG (152), ETV1 (28), ETV4 (14), SPOP (37), other (86)	*
STAD	277	CIN (138), EBV (25), GS (54), MSI (60)	*

BLCA: Bladder Urothelial Carcinoma, BRCA: Breast invasive carcinoma,
COAD: Colorectal adenocarcinoma, PRAD: Prostate adenocarcinoma,
STAD: Stomach adenocarcinoma

* Sources of data set: BLCA (Robertson *et al.* (2017)), COAD (Guinney *et al.* (2015)), PRAD (Abeshouse *et al.* (2015)), STAD (Network *et al.* (2014))

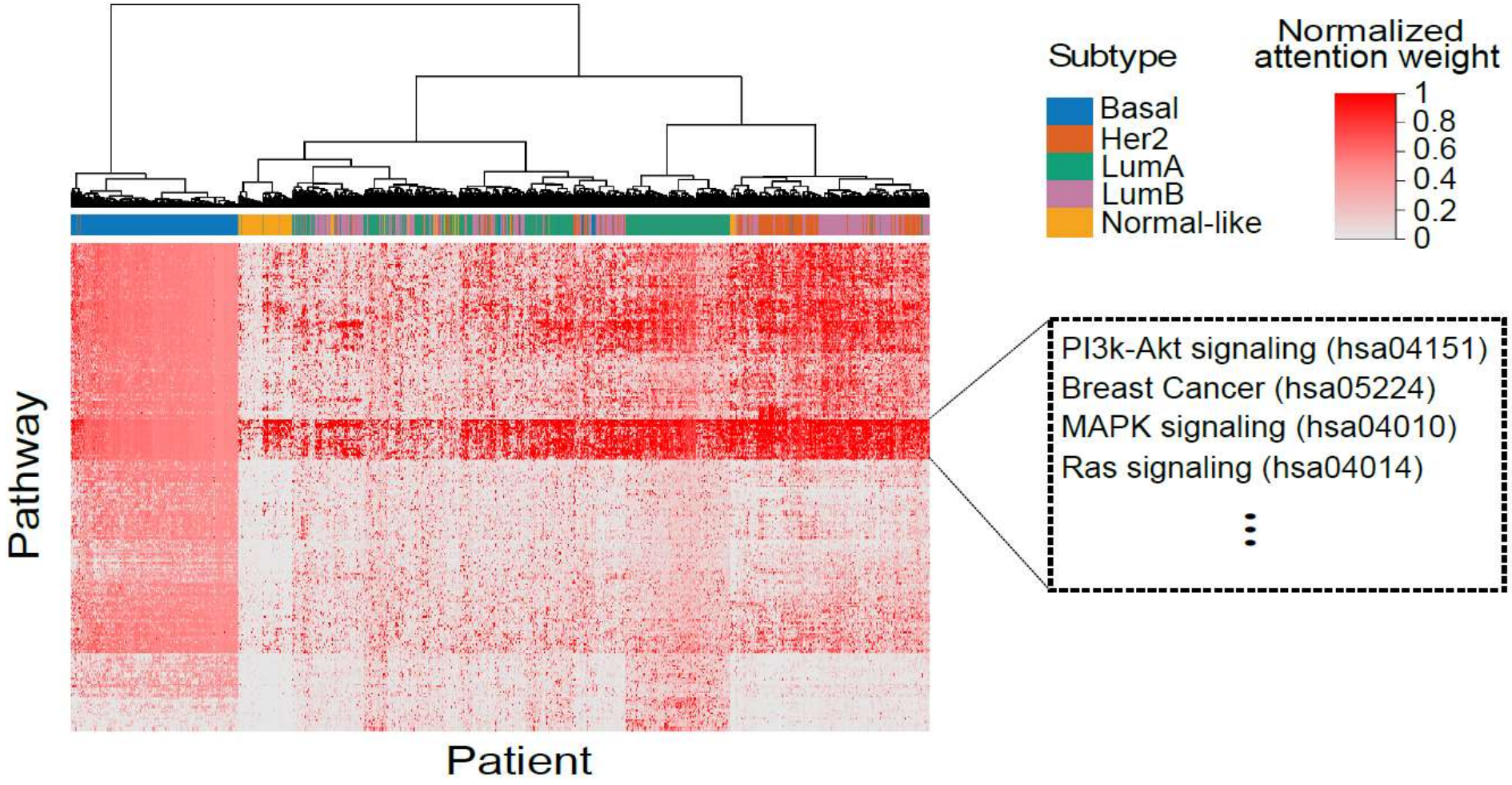
** The subtypes of breast cancer samples were classified using RNA-seq data and PAM50 as mentioned in the Section 2.4.

Performance comparison of Proposed model

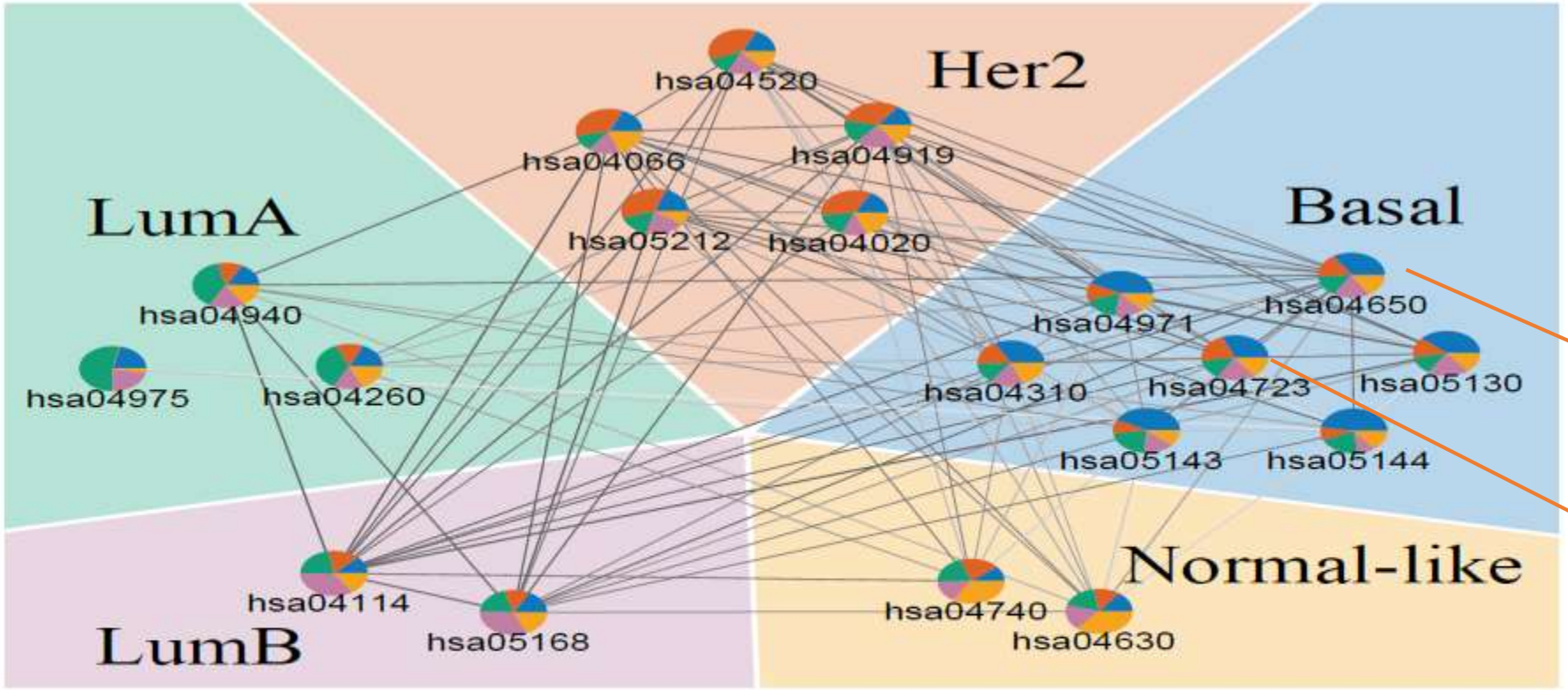
	BLCA	BRCA	COAD	PRAD	STAD
GCN+MAE (best)	**93.74** (9-Att)	**85.52** (14-Att)	**87.01** (11-Att)	**89.62** (9-Att)	**91.49** (7-Att)
GCN+MAE (#class-Att)	93.48	85.22	86.25	88.52	90.8
GCN+ *Single Att	91.08	85.03	84.97	86.55	90.96
GCN best	90.98 (hsa04151)	82.72 (hsa05206)	82.79 (hsa04151)	86.13 (hsa05200)	90.79 (hsa04151)
†SAS+SVM	81.51	74.41	77.54	79.25	76.08
SAS+RF	79.12	73.54	69.44	67.02	67.00
SAS+MLP	83.27	48.51	76.40	77.52	76.82
‡RAW+SVM	89.18	82.62	78.41	82.58	86.39
RAW+RF	79.83	77.11	74.69	68.36	76.17

* Instead of multi-attention, the GCN pathway models are combined with single attention mechanism
† The pathway activity inference tool from Lim *et al.* (2016)
‡ 20,531 genes are used as input features
hsa04151: PI3K-Akt singnaling pathway
hsa05206: MicroRNAs in cancer
hsa05200: Pathways in cancer

Heatmap of the attention weight of GCN+MAE model on BRCA data.



Pathway Network for BRCA subtypes by Network propagation

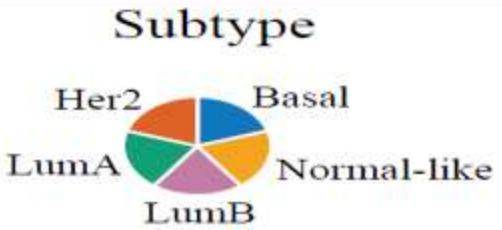


Natural killer cell mediated cytotoxicity

Rescued by Network propagation

Retrograde endocannabinoid signaling

- Apoptosis
- Proliferation
- Neovascularization and angiogenesis
- Metastasis formation
- Autophagy



Conclusion

- Two major challenges in modeling cancer subtypes with pathways.
  - Pathway is represented as a form of graph that is **not suitable for further computational analysis.**
  - Pathway is **a small component** of biological processes that manipulate the behavior of cells.
- To address the challenges, we present an ensemble based pathway model with attention mechanism and network propagation technique.
  - extracting and encoding biological knowledge by Graph Convolutional Network
  - reconstructing biological processes in comprehensive scale by Multi-attention base ensemble
  - mining significant pathways with interaction information by Network propagation
- In experiments with five TCGA cancer data sets, our model demonstrated very good performance in cancer subtype classification.
- In addition to the subtype classification, our method showed subtype-specific pathway interaction networks as a result of using *attention mechanisms* and *pathway propagation*.

PRISM:
Methylation Pattern-Based, Reference-free Inference of Subclonal Makeup

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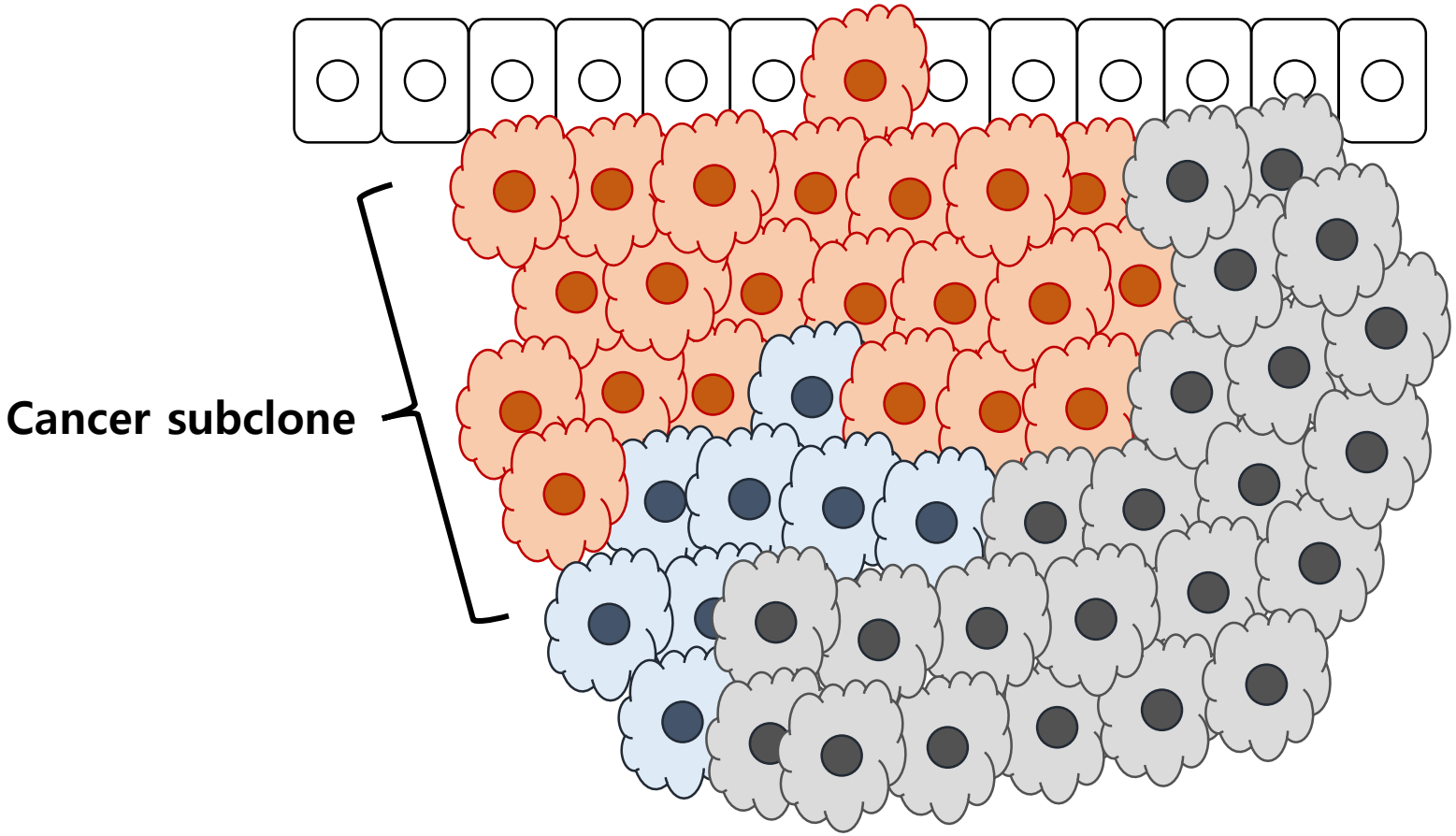
Bio & Health Informatics Lab.

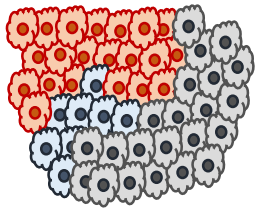
PRISM: Methylation Pattern-based, Reference-free Inference of Subclonal Makeup

- What to do:
  - Decomposing (clustering) very high dimensional data, (> 50 millions dimensions)
- How to do this:
  - Curse of high dimensionality
  - Blessing of very high dimensionality (biology domain specific)
    - Maybe, works for more general settings of "decomposing event sequence on very high dimensions"
    - Discard dimensions that we cannot deal with.
    - Use the remaining dimensions only. (**reminiscence of clusters on each dimension)**
    - Since dimensions are very high, we have enough information to decompose data.

Intratumoral heterogeneity



Subclonal inference



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+SRR038845.3 HWI-EAS038:6:1:0:1938 length=36
BA@7>B=>:>>7@7@>>9=BAA?;>52;>:9=8.=A
@SRR038845.41 HWI-EAS038:6:1:0:1474 length=36
CCAATGATTTTTTTCCGTGTTTCAGAATACGGTTAA
+SRR038845.41 HWI-EAS038:6:1:0:1474 length=36
BCCBA@BB@BBBBAB@B9B@=BABA@A:@693:@B=
@SRR038845.53 HWI-EAS038:6:1:1:360 length=36
GTTCAAAAAGAACTAAATTGTGTCAATAGAAAACTC
+SRR038845.53 HWI-EAS038:6:1:1:360 length=36
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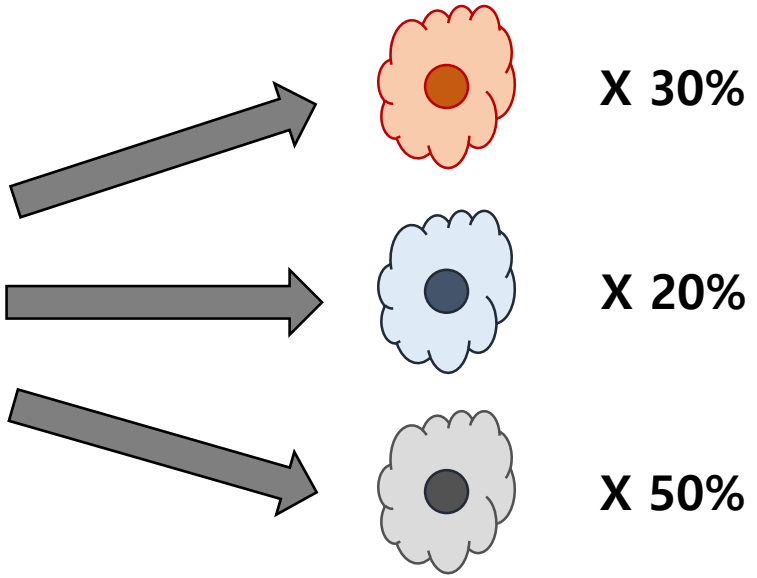
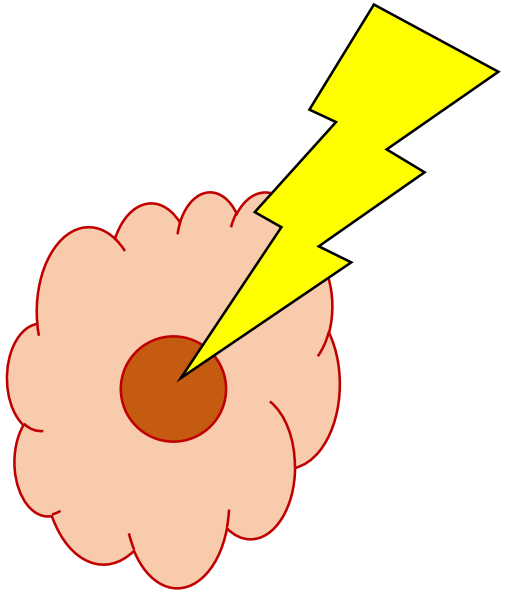


PRISM uses subclonal methylation signatures for subclonal inference



Global DNA methylation reprogramming

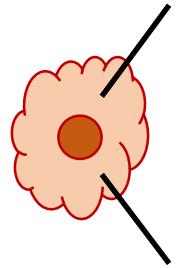
Problem

- GOAL: Inferring subclonal structure of a tumor with DNA methylation patterns

- INPUT: A collection of DNA methylation patterns of a tumor
  - sequenced by RRBS

- OUTPUT: Inferred counts and size of constituent subclones

Viewing cell as vector of binary patterns



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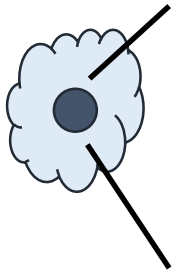

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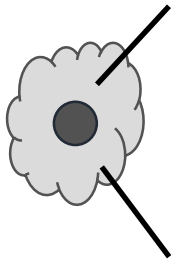

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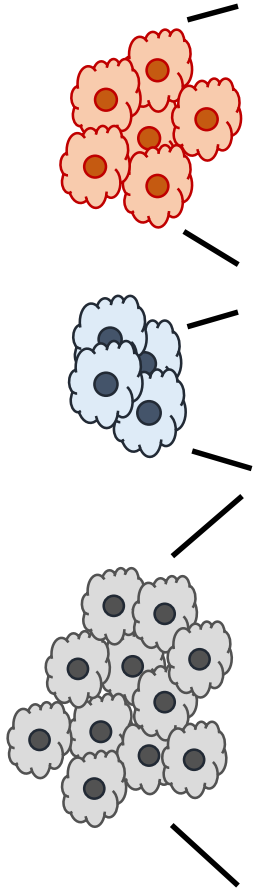
Viewing cell as vector of binary patterns



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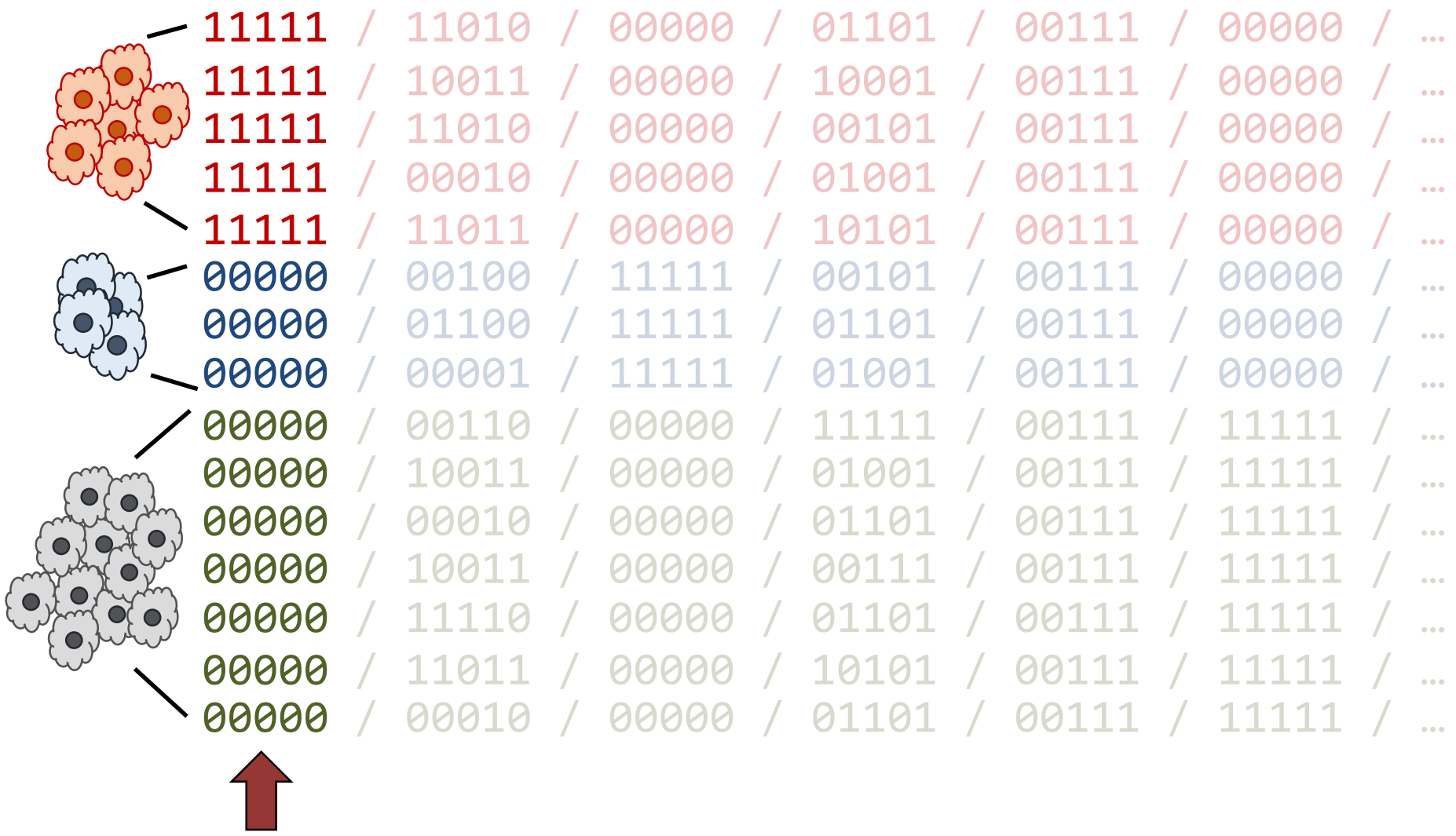
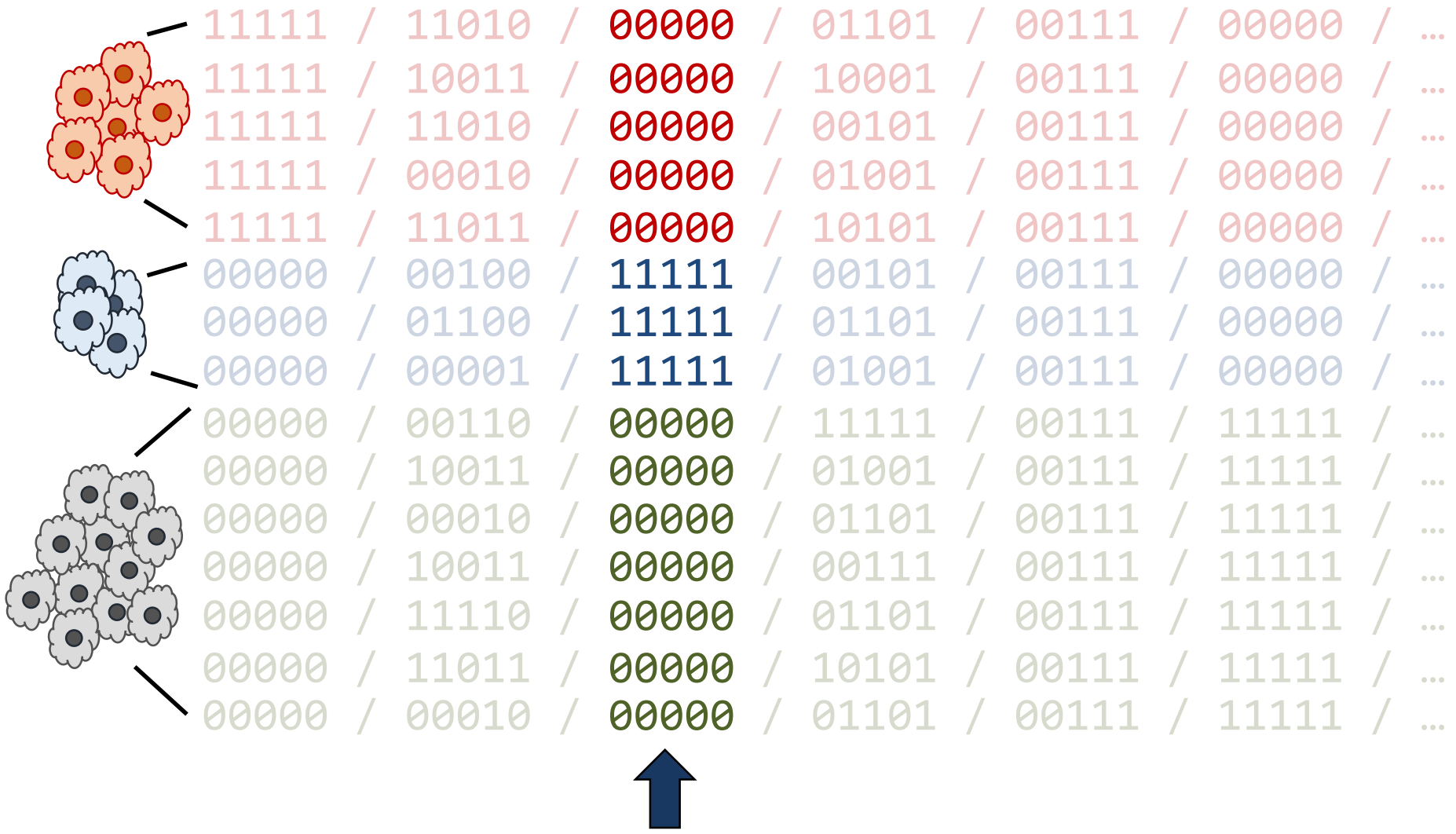
Fingerprint epilocus



Fingerprint epilocus for red subclone

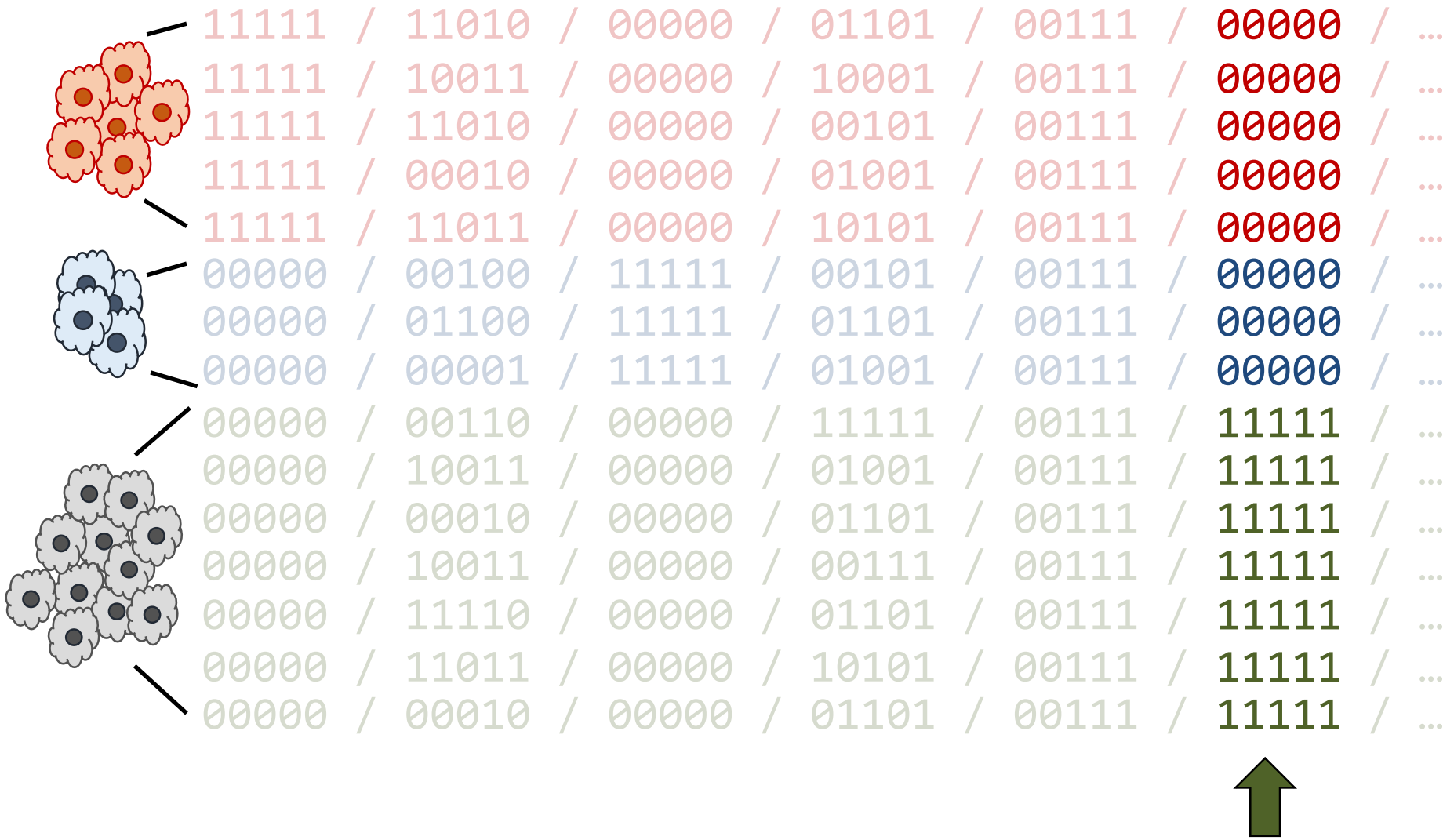
Fingerprint epilocus

Fingerprint epilocus



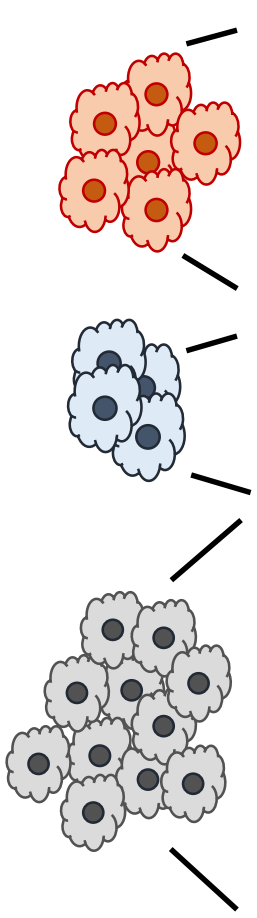
Fingerprint epilocus for blue subclone

Fingerprint epilocus



Fingerprint epilocus for green subclone

Sequencing = random sampling of patterns



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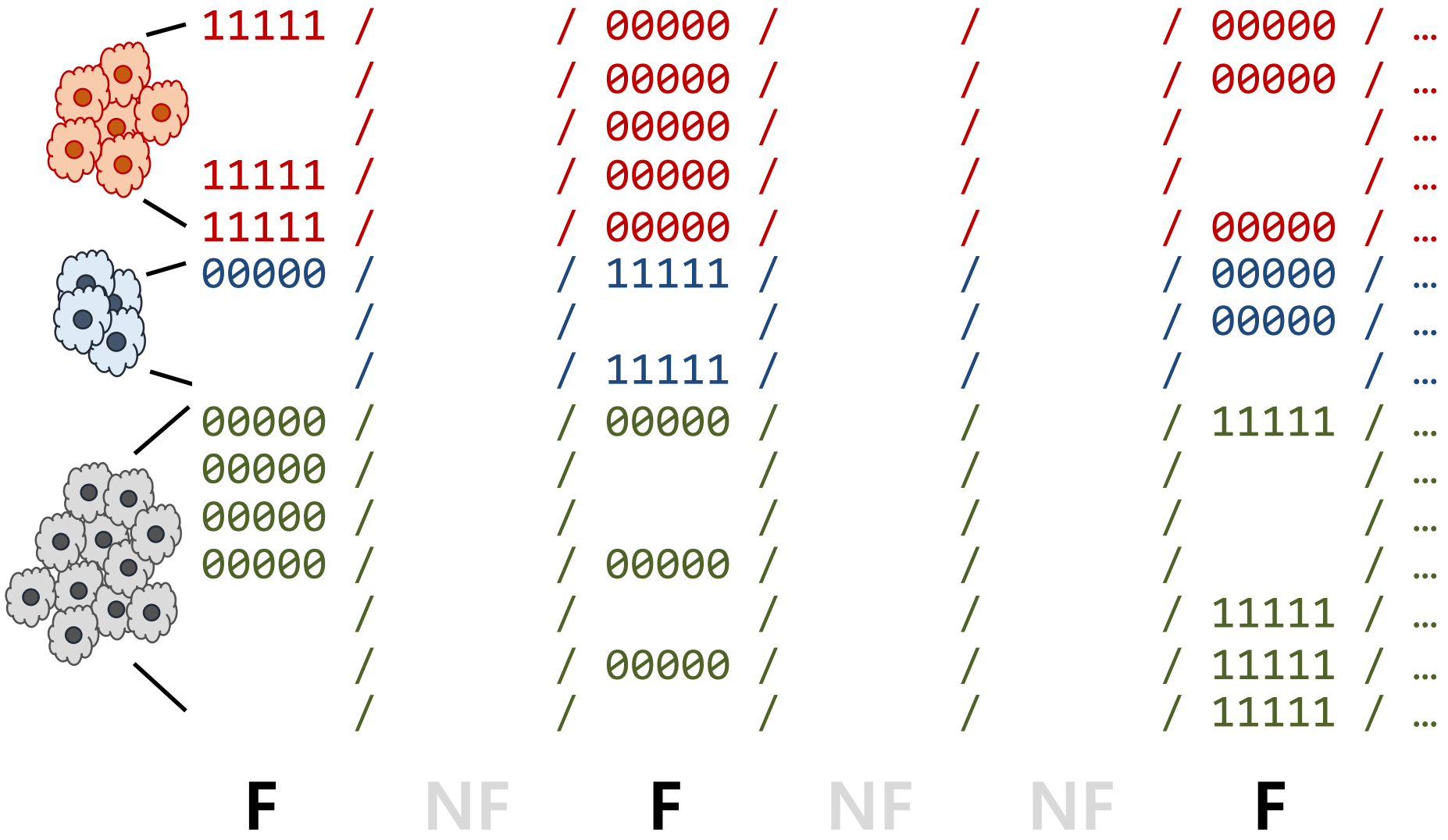
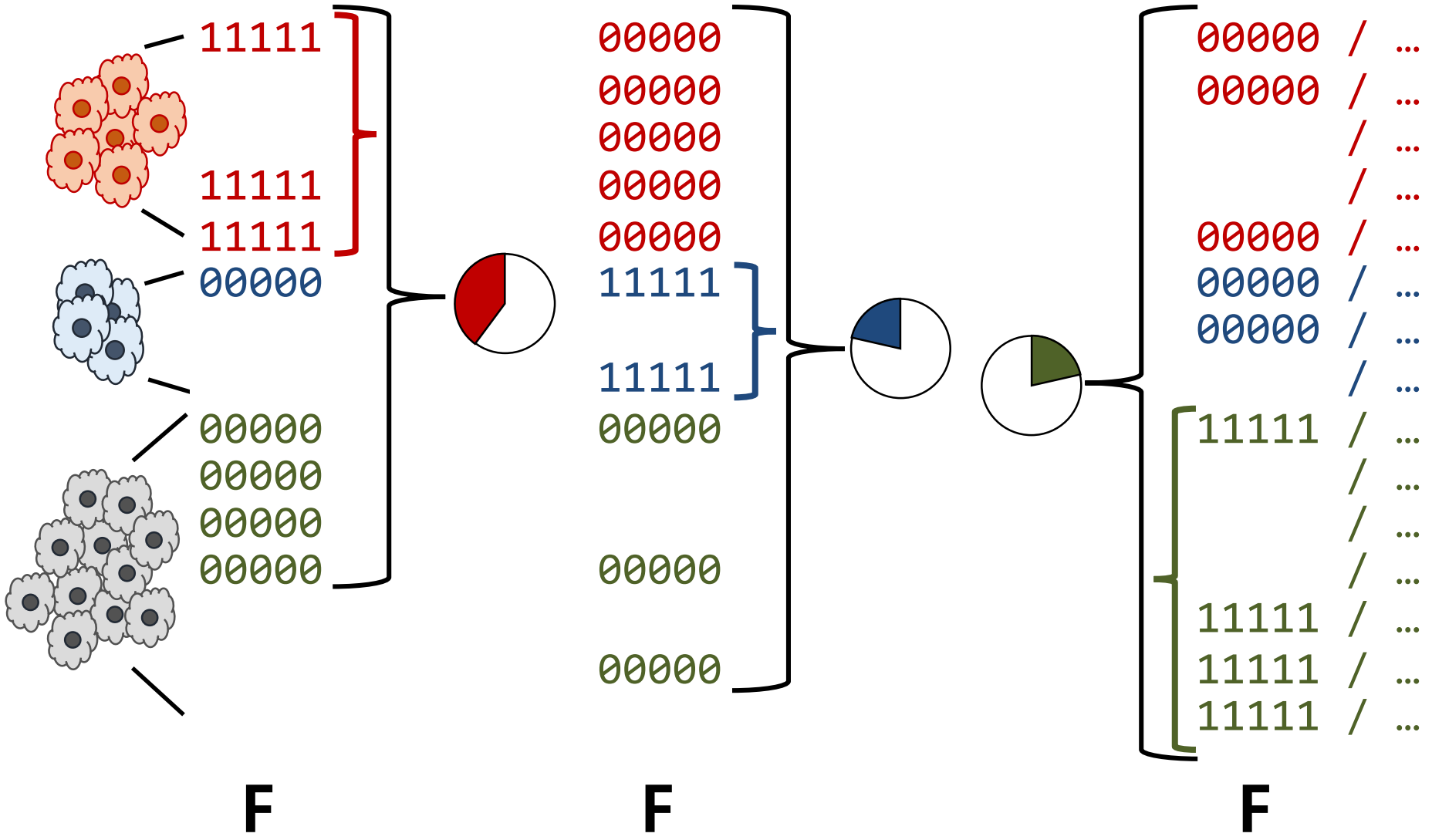
Sequencing = random sampling of patterns

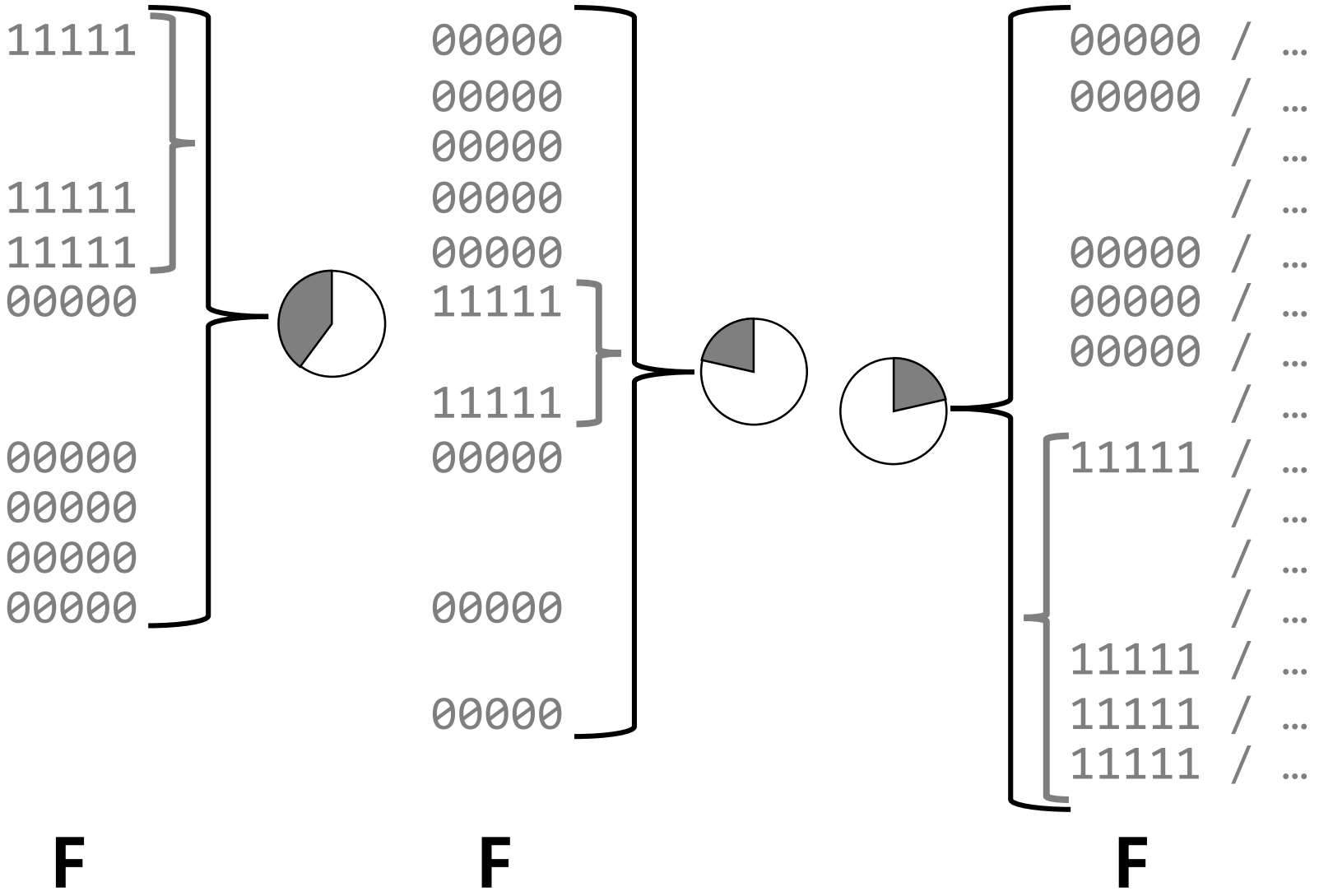
PRISM ignores non-fingerprint epiloci



Fraction of fingerprint reflects subclonal prevalence



In fact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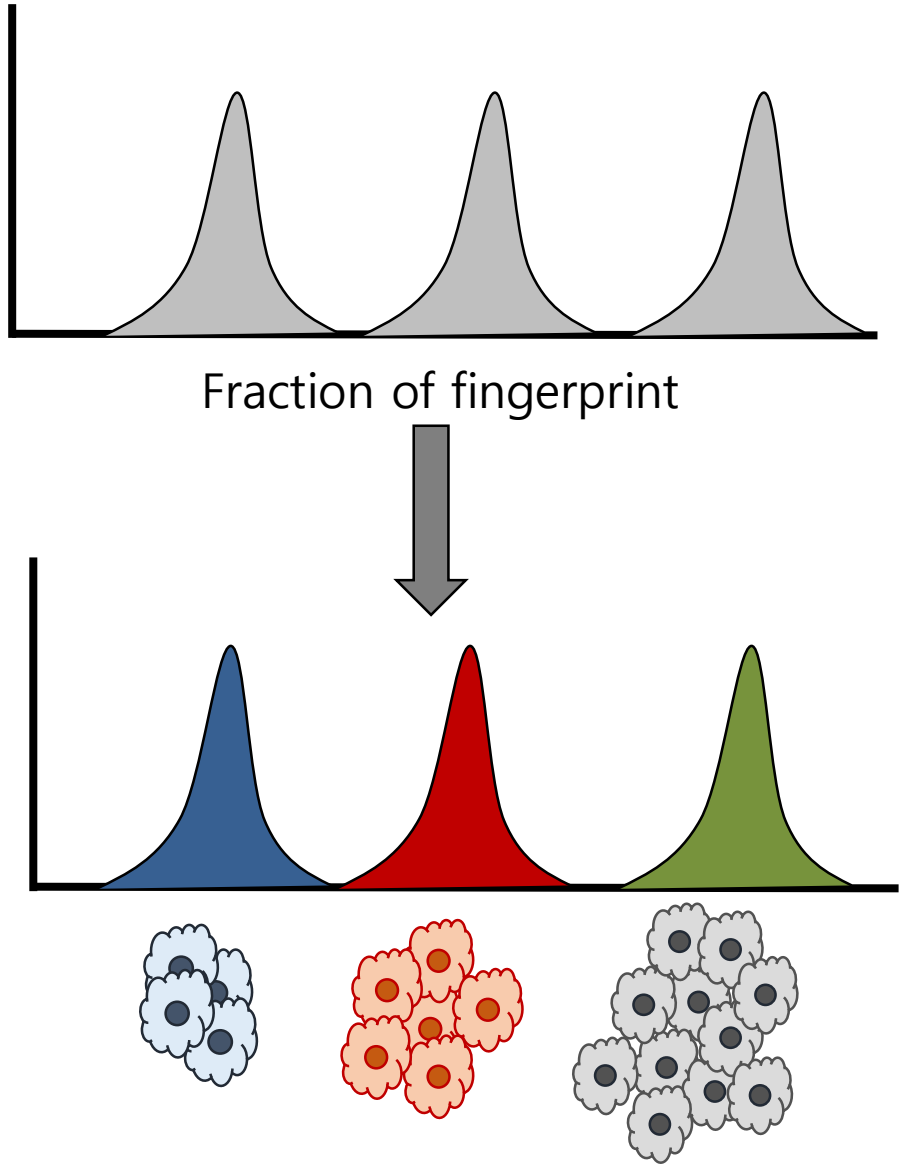
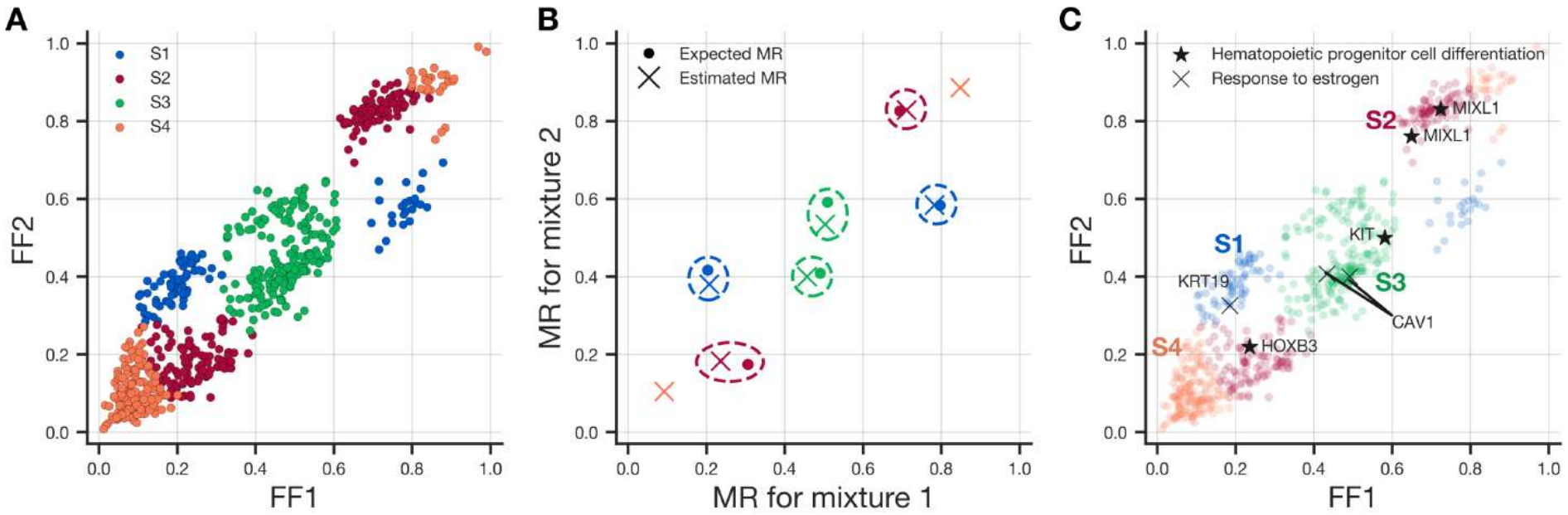
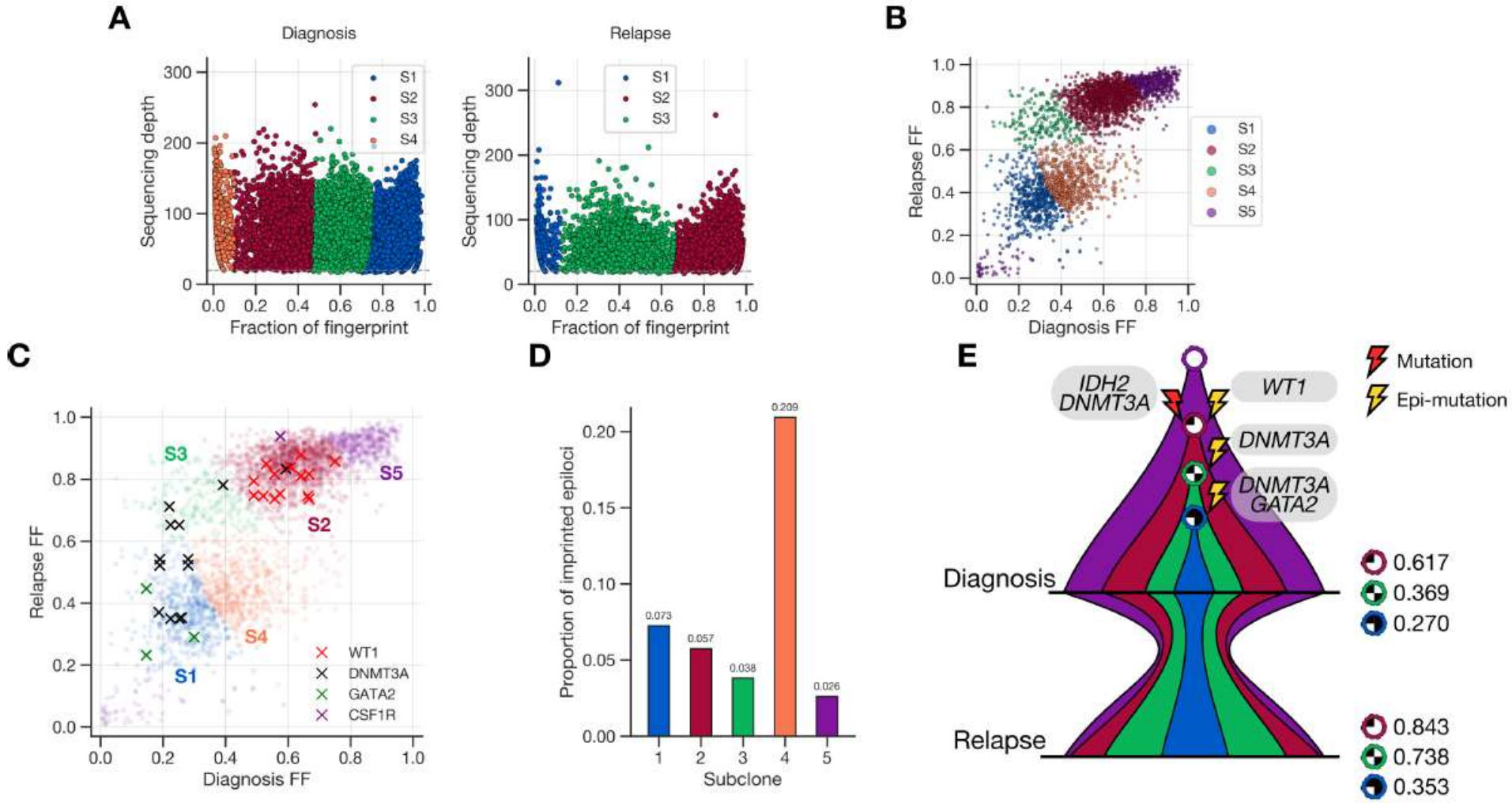
Clusters are identified by solving mixture model



Simulated cell line mixtures



Analyzing AML diagnosis-relapse pair



Conclusion

- PRISM focuses on **fingerprint epiloci** whose ratio represents the prevalence of the corresponding subclone.
- DNMT1-like HMM-based *in silico* proofreading calibrates the subclone size estimates.
- Whether the the genomic and epigenomic evolution occur coordinately or independently is still obscure, and even seem to be case-dependent.
- PRISM offers the mean to obtain high-resolution "epigenomic" evolutionary history.
- Along with the result of "genomic" subclonal inference, multi-omics intratumor heterogeneity can be assessed.

2019 DAY1

Thank you!