Learning Feature Importance for a Deep Learning Cancer Classifier

Jacob Chmura
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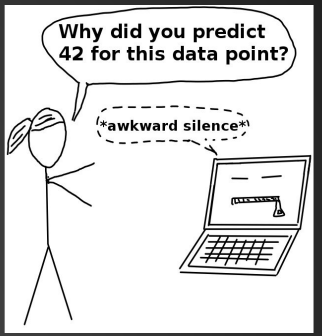
Supervisor: Quaid Morris
University of Toronto Undergraduate Summer Research Program

Lack of Interpretability in Deep Learning is a Limitation



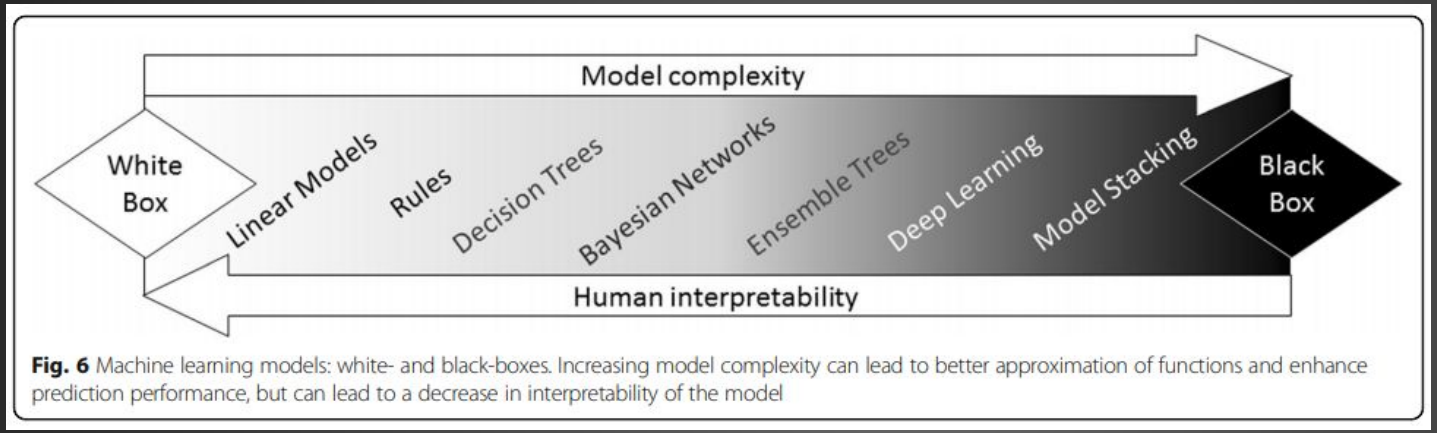


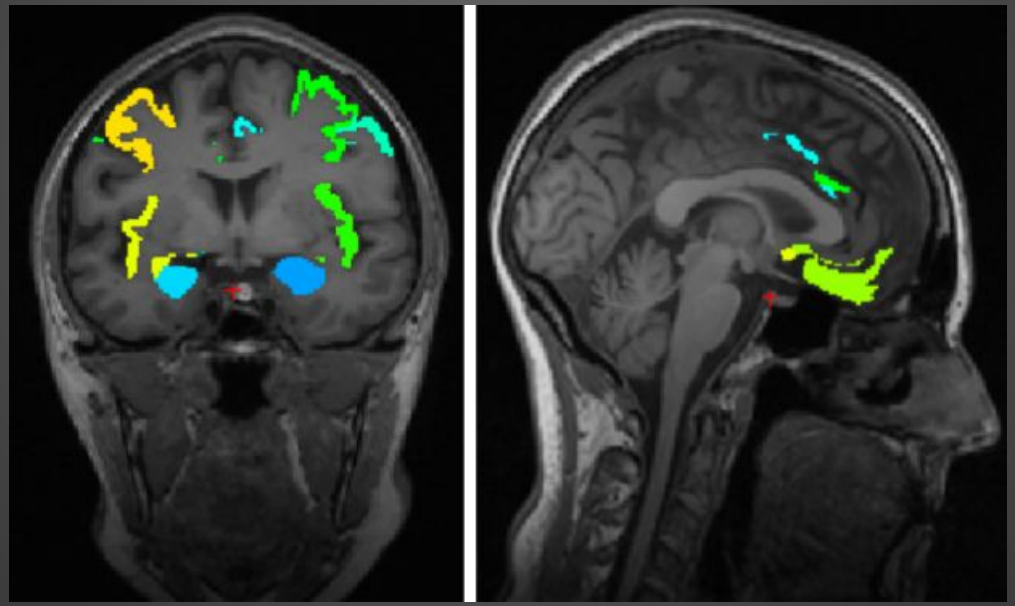
Fig. 6 Machine learning models: white- and black-boxes. Increasing model complexity can lead to better approximation of functions and enhance prediction performance, but can lead to a decrease in interpretability of the model

https://onehealth.ifas.ufl.edu/media/onehealthifasufledu/pdfs/publications/Prosperi-article.pdf

- *Object recognition network*: could tell us which pixels of the image responsible for a label being picked

Lack of Interpretability in Deep Learning is a Limitation

- *Medical imaging model*: could help inform the doctor of the part of the image that resulted in the recommendation. Knowing the strengths and weaknesses of a model is essential in clinical settings.



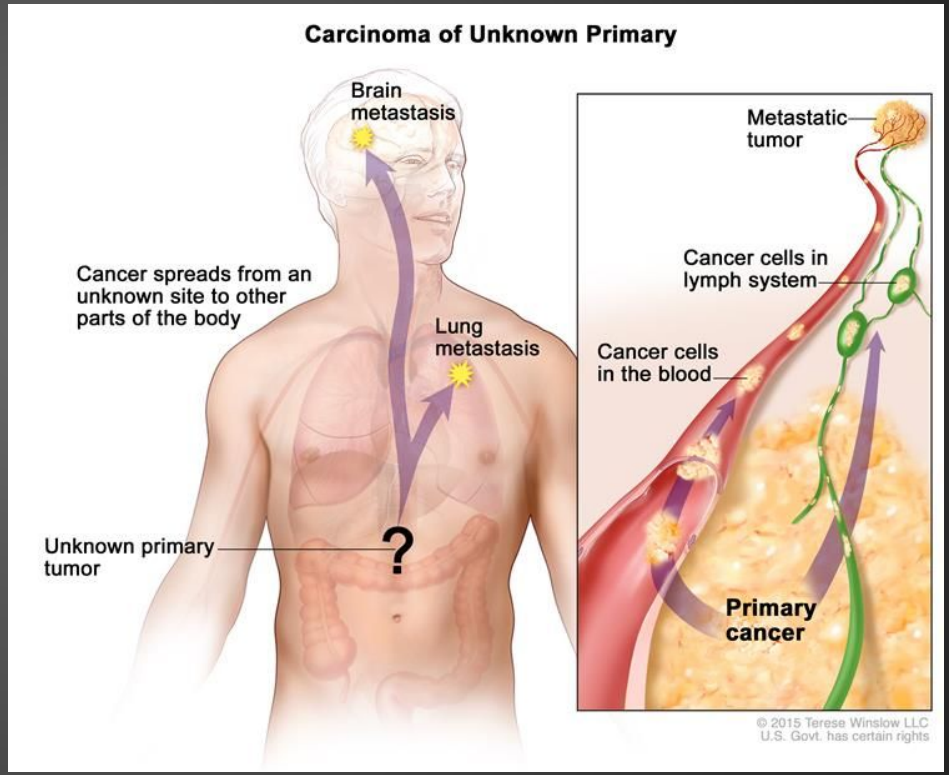
Classifying Primary and Metastatic Cancers based on Mutation Patterns using Deep Learning Techniques

Situation:

- pathologist can't identify primary cancer tumor well
- at autopsy, the primary cannot be identified roughly 70% of the time
- fourth most common cause of cancer death
- therapeutic options are driven by tissue of origin

Idea:

- Different tumour types have dramatically different patterns of mutation
- Use this to train a deep network to classify cancer classes



https://www.cancer.gov/types/unknown-primary/patient/unknown-primary-treatment-pdq

Features for the Model

~ 5000 length feature vector split into three main categories:

(1) *Mutation Distribution (~3000)*: encode information about cell type

- divided genome into bins and created features corresponding to the number of mutations per bin

Wild type gene	C G A C T G G C T G A C
Transition (AT pair replaced by GC pair)	C G **G** C T G G C **C** G A C
Transversion (AT pair replaced by TA pair)	C G **T** C T G G C **A** G A C
Insertion (GC pair inserted)	C G A **G** C T G G C T **C** G A C
Deletion (AT pair deleted)	C G C T G G C G A C

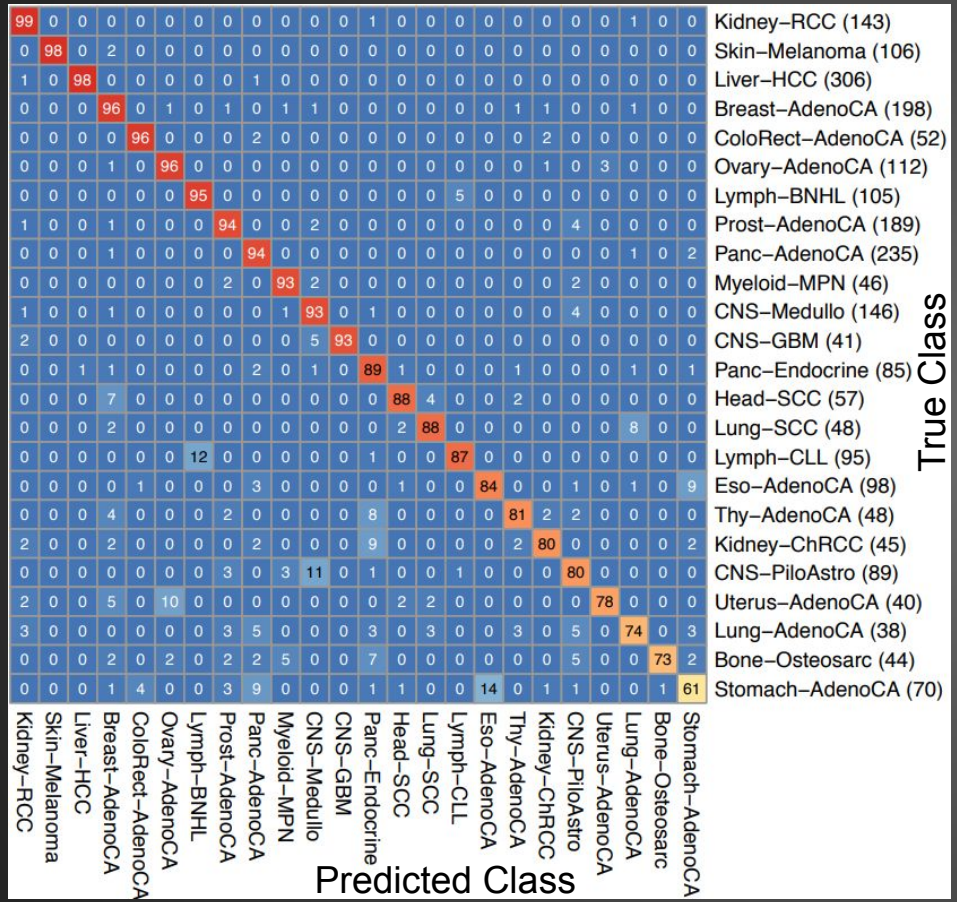
http://www.biochem.uthscsa.edu/med/06-Mechanisms-of-Mutation/PrereqMechanismsofMutation_print.html

(2) *Mutation Types (~150)*: reflect environmental exposures of the cell of origin

- Ex. skin cancers have mutation types strongly correlated with UV light-induced DNA damage.

(3) *Driver Genes (~2000):* tumour types are distinguished by high frequencies of alterations in particular driver genes and pathways

Results



- classifier achieves an accuracy of 91%
- most frequent classification errors for Stomach-AdenoCA samples were two other upper gastrointestinal tumours, (Eso-AdenoCA and Panc-AdenoCA)

(Wei Jiao et al., 2019)

Goals

- *Aim 1:* take existing model and assess feature importance

- *Aim 2*: produce certainty estimates and extend to rare cancer types

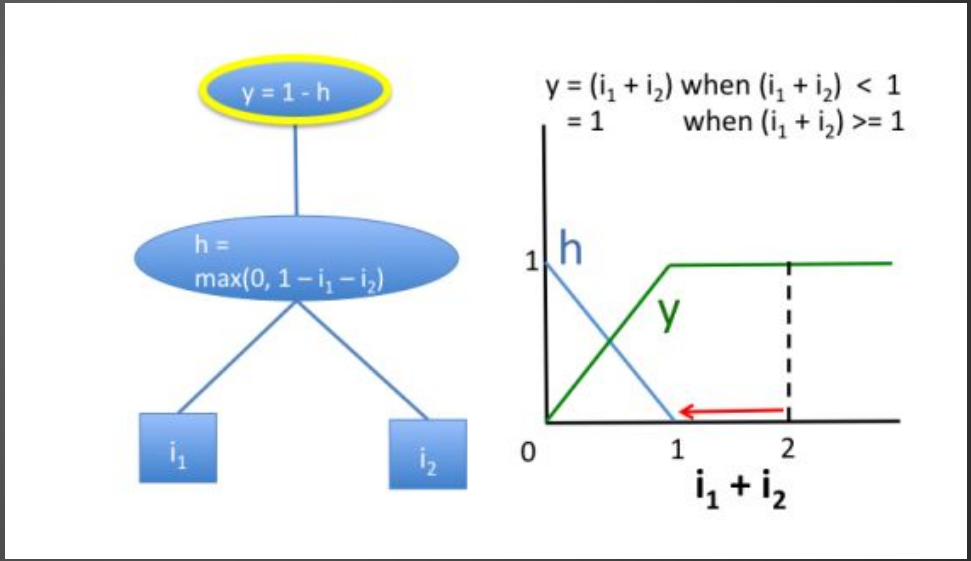
How do we learn which features are important?

Idea 1: *Perturbations*?

- Make small changes to individual inputs and observe the impact on later neurons in the network

Problems:

- computationally inefficient
- **Saturation problem**



(Avanti Shrikumar, 2017)

***Saturation problem**:* lack of local change need not imply zero importance

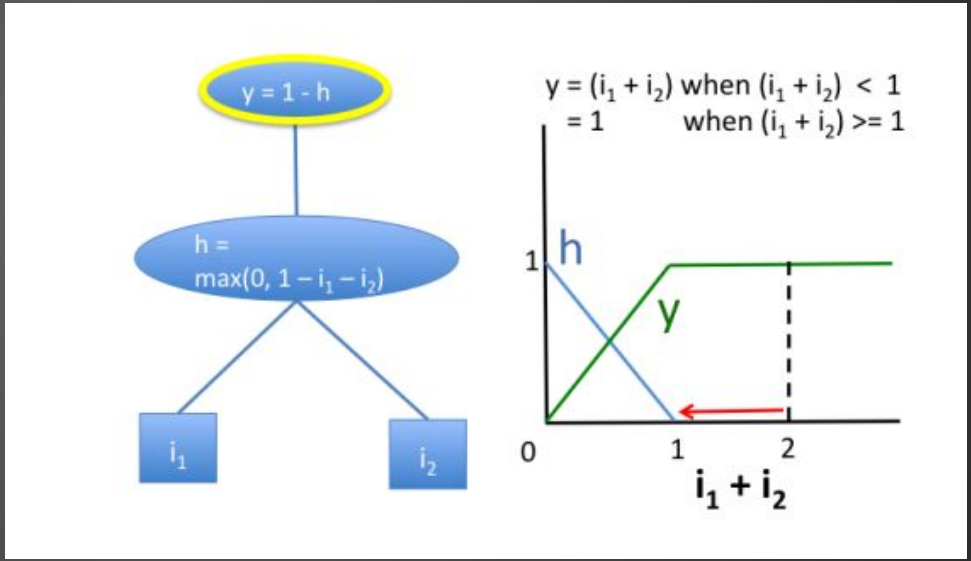
How do we learn which features are important?

Idea 2: *Gradients*?

- Compute the gradient of the outputs with respect to each input feature

Problems:

- nonlinearities
- **Saturation problem**



(Avanti Shrikumar, 2017)

***Saturation problem**:* lack of local change need not imply zero importance

DeepLIFT (Deep Learning Important FeaTures) *(Avanti Shrikumar, 2017)*

Philosophy: explain the difference in output from some ‘reference’ output in terms of the difference of the input from some ‘reference’ input.

reference input: represents default or *neutral* baseline that is chosen

- references for all neurons can be found by choosing a reference input and propagating activations through the net

- t represents target output neuron of interest
- $x_1, x_2, ..., x_n$ represent neurons in some intermediate layer
- t_0 represent the reference activation of t.
- Δt is difference-from-reference, that is $\Delta t = t - t_0$.

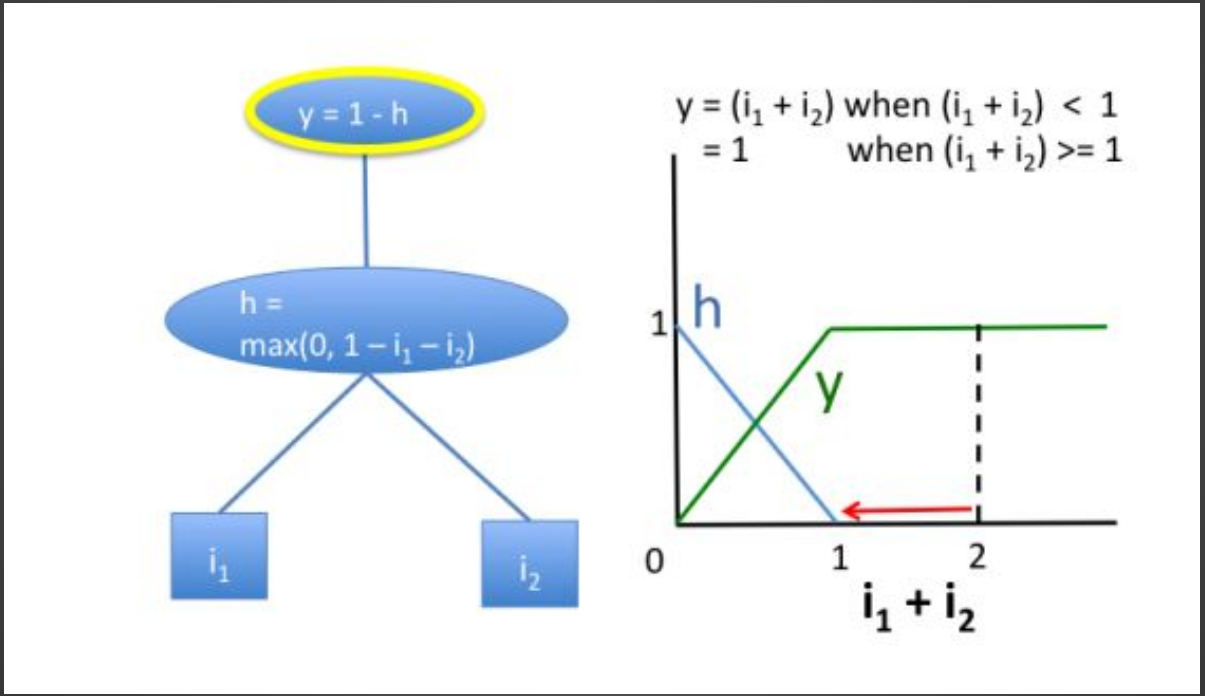
$$\sum_{i=1}^{n} C_{\Delta x_i \Delta t} = \Delta t$$

DeepLIFT assigns contribution scores:

- $C_{\Delta x_i \Delta t}$ is the amount in t that is *blamed* on difference-from-reference of x_i .

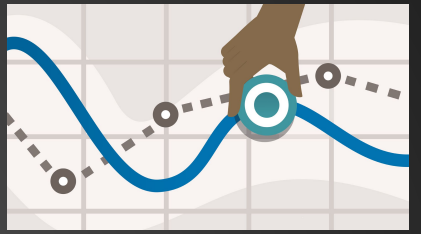
Saturation Problem Revisited

- C∆xi∆t can be non-zero even when ∂t / ∂xi is zero: a neuron can be signaling meaningful information even when its gradient is zero.



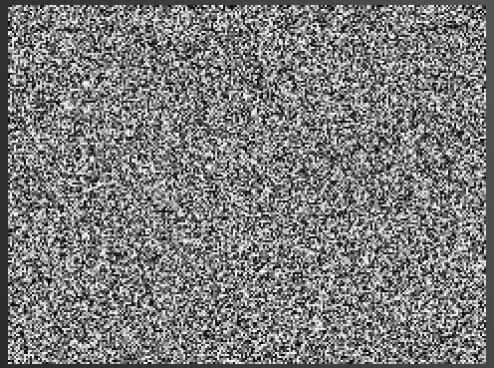
- DeepLIFT is sensitive to chosen reference

Important Question: *How do we choose a good reference?*



Intuition: ask ourselves *what am I interested in measuring differences against?*

- needs to convey a complete absence of signal (allows us to interpret the attributions as a function of the input)



black image or noisy image signifies the absence of objects

zero embedding vector is a good baseline

Choosing a reference for Cancer Classifier

~ 5500 length feature vector split into three main categories:

Mutation Distribution (~3000)	Mutation Type (~150)	Drivers (~2000)

★ Typical Feature Vector is extremely sparse

Null Reference

- A vector of all zeros

0 0 0 … 0 0 0	0 0 0 … 0 0 0	0 0 0 ... 0 0 0

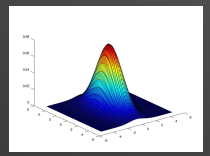
Shuffle Reference

- permute within the three main sections of the input vector and averaging the results over multiple such references

1.1 -1.6 … 0.7 0.2	0.0 0.5 … 1.1 -0.7	2.9 1.3 … 2.1 0.2

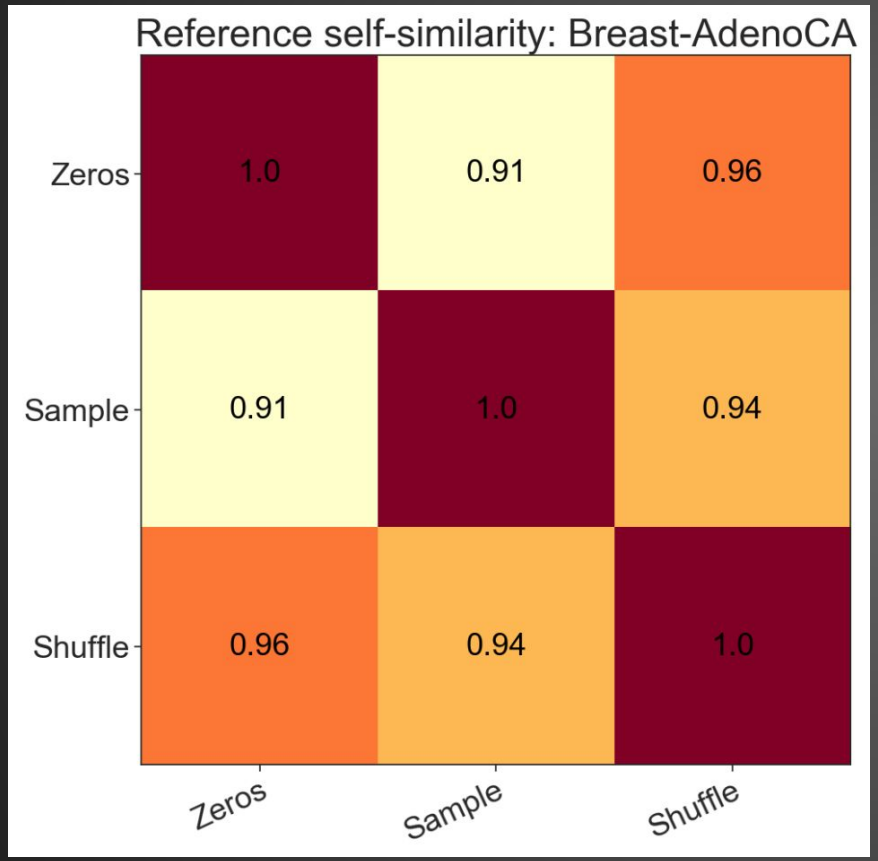
Sample Reference

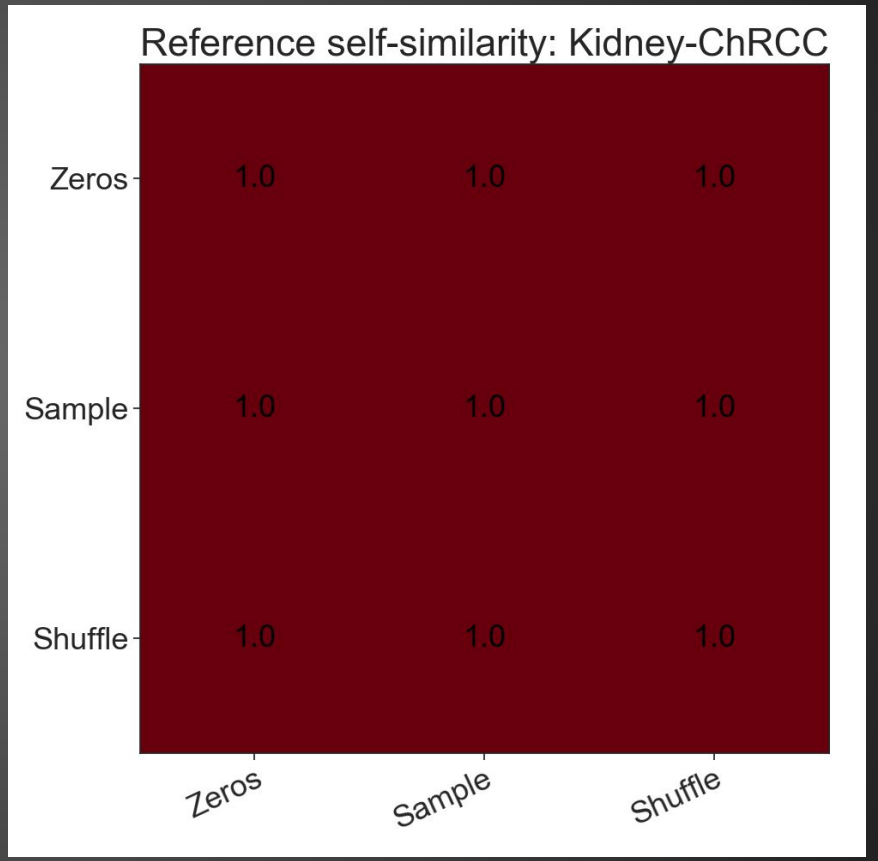
- For each z score feature, simply sample from a Gaussian
- For count features, create a distribution of frequencies and sample from it



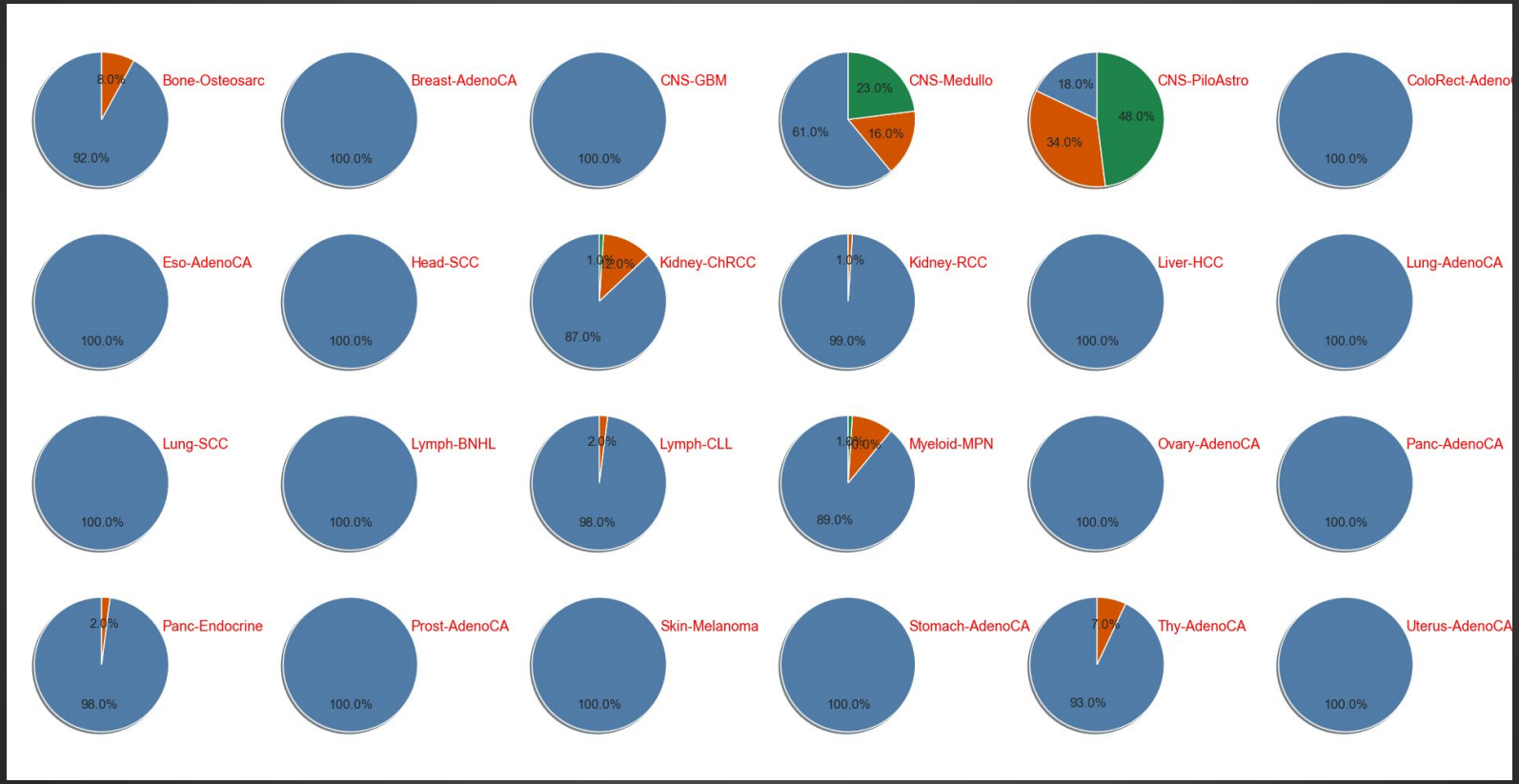
2.1 -0.6 … -1.7 0.1	0.0 3.5 … 0.1 0.7	1.9 1.3 … 2.1 0.2

Reference Self-Similarity Matrix

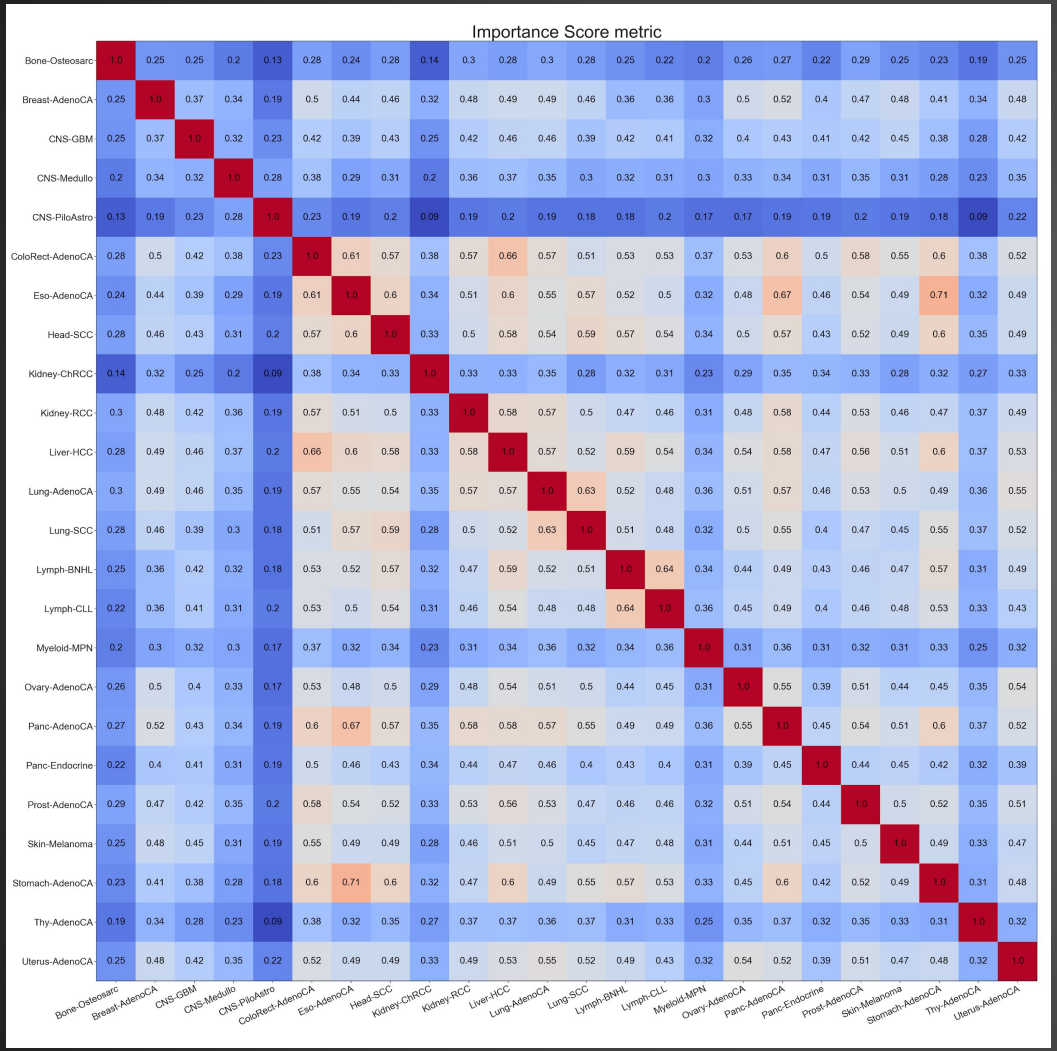




Feature Type Distribution over 100 Most Significant Inputs



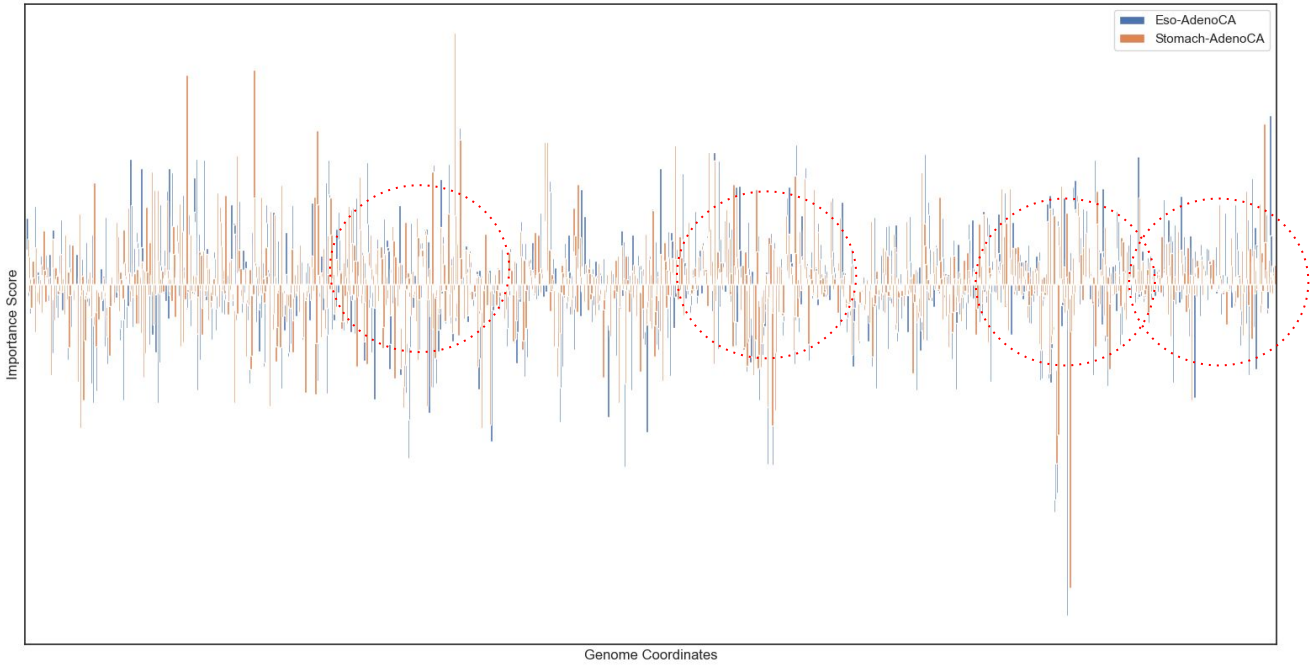
Retraining without driver features, the classifier does just as good



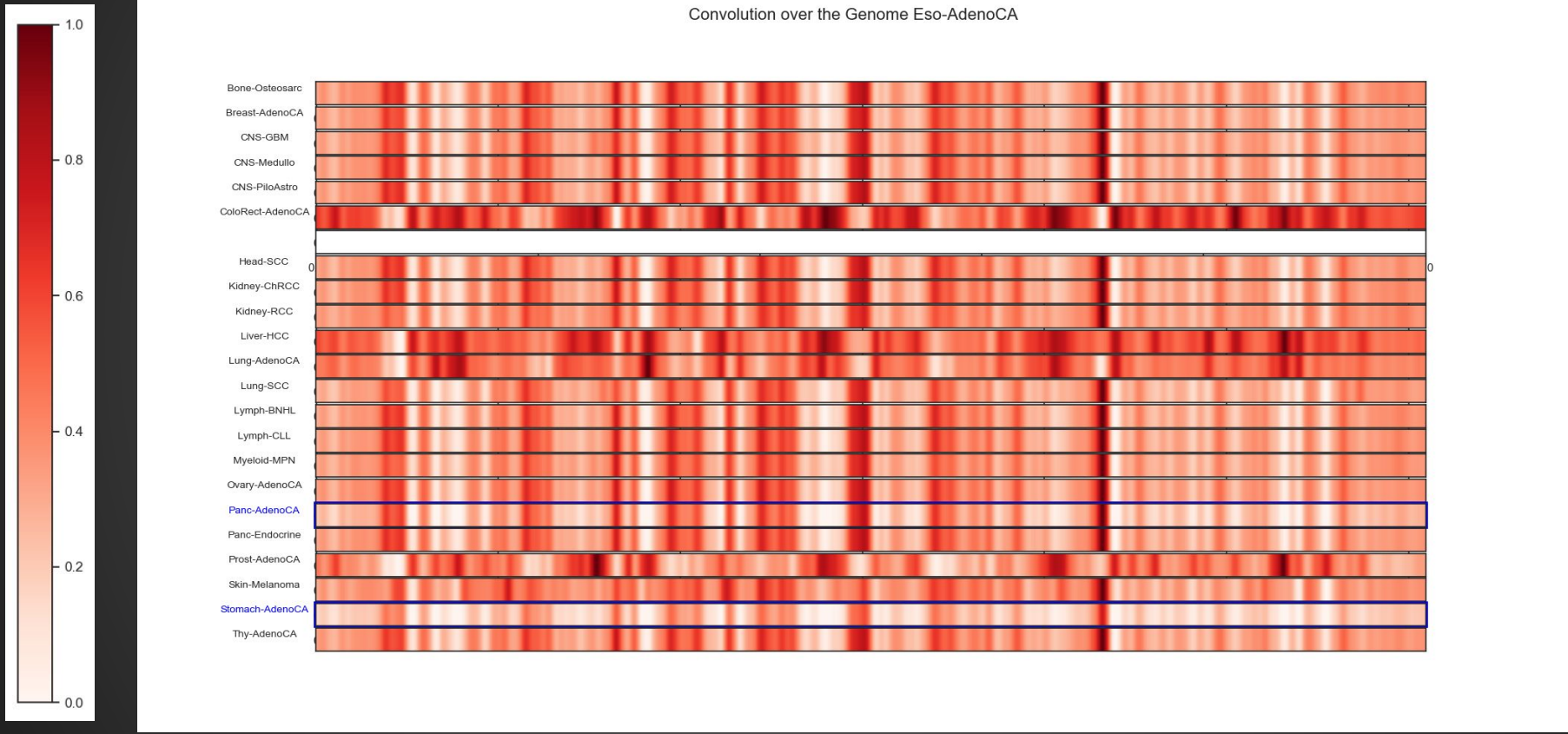
Cancer class Self-Similarity over 100 Most Significant Input Features

- Similarity score computed using adaptation of Jaccard Index over feature importance
- No drivers
- Average of all 3 references

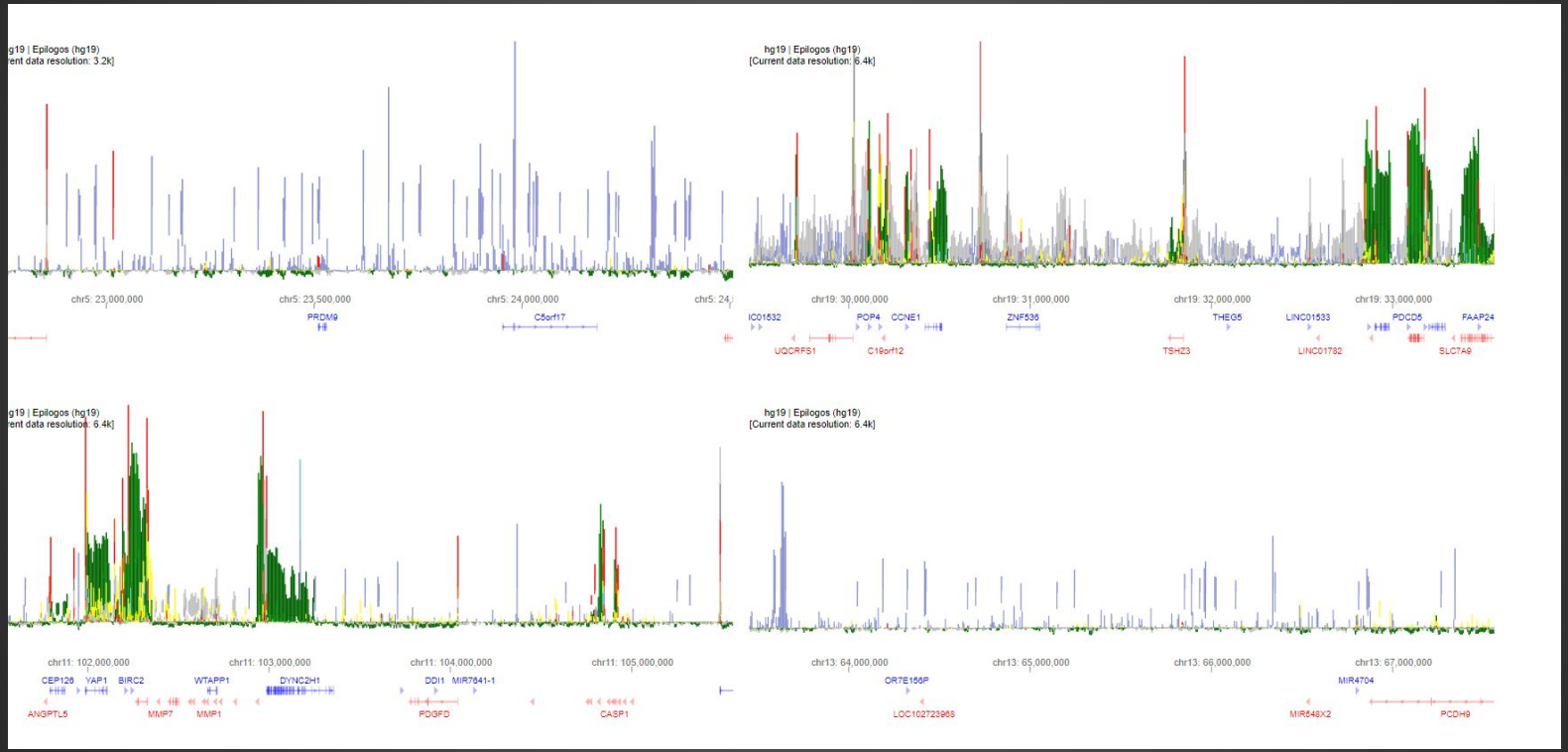
Genome Wide Mutation Importance: Chromosome 11-15



Convolution of Importance Scores Across Genome

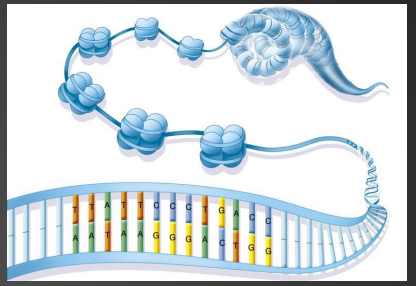


Genome Annotation Process: *Extract genes from most important DeepLIFT scoring genome regions*



Bone-Osteosarc Important Regions

Chromatin States Extraction Controlled for Cell Type



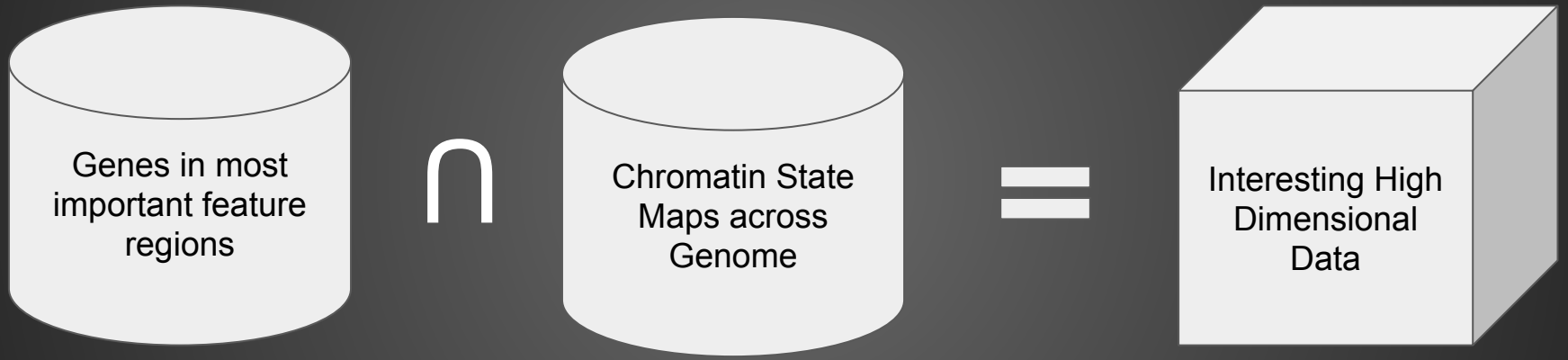
- Chromatin is understood to be a complex genome organizer
- Map chromatin function along the genome to discrete states

Does it transcribe?

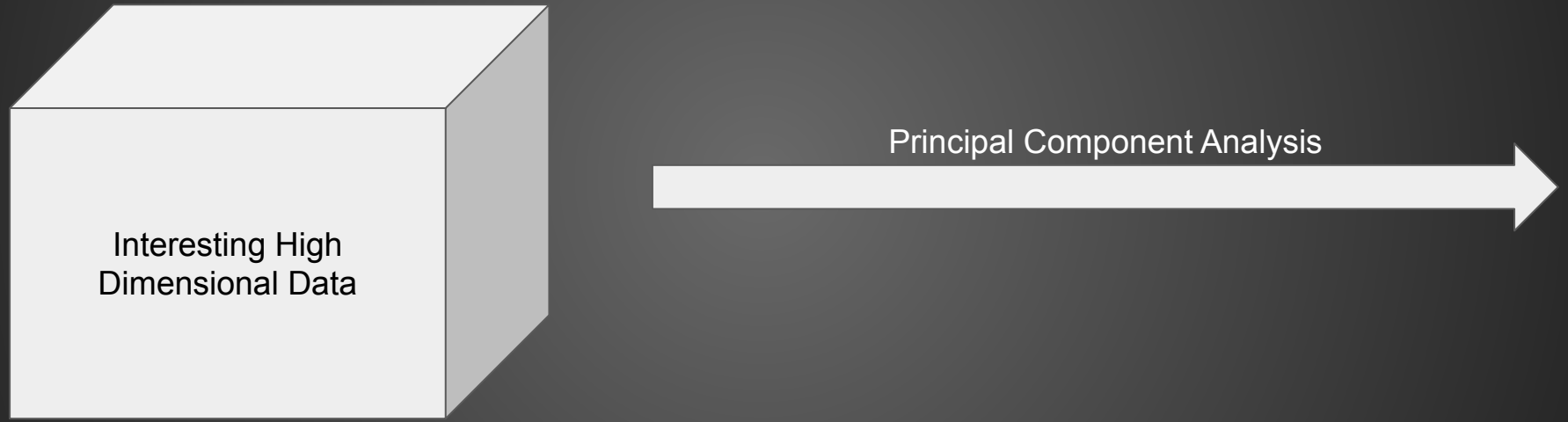
STATE NO.	MNEMONIC	DESCRIPTION	COLOR NAME	COLOR CODE
1	TssA	Active TSS	Red	255,0,0
2	TssAFlnk	Flanking Active TSS	Orange Red	255,69,0
3	TxFlnk	Transcr. at gene 5' and 3'	LimeGreen	50,205,50
4	Tx	Strong transcription	Green	0,128,0
5	TxWk	Weak transcription	DarkGreen	0,100,0
6	EnhG	Genic enhancers	GreenYellow	194,225,5
7	Enh	Enhancers	Yellow	255,255,0
8	ZNF/Rpts	ZNF genes & repeats	Medium Aquamarine	102,205,170
9	Het	Heterochromatin	PaleTurquoise	138,145,208
10	TssBiv	Bivalent/Poised TSS	IndianRed	205,92,92
11	BivFlnk	Flanking Bivalent TSS/Enh	DarkSalmon	233,150,122
12	EnhBiv	Bivalent Enhancer	DarkKhaki	189,183,107
13	ReprPC	Repressed PolyComb	Silver	128,128,128
14	ReprPCWk	Weak Repressed PolyComb	Gainsboro	192,192,192
15	Quies	Quiescent/Low	White	255,255,255

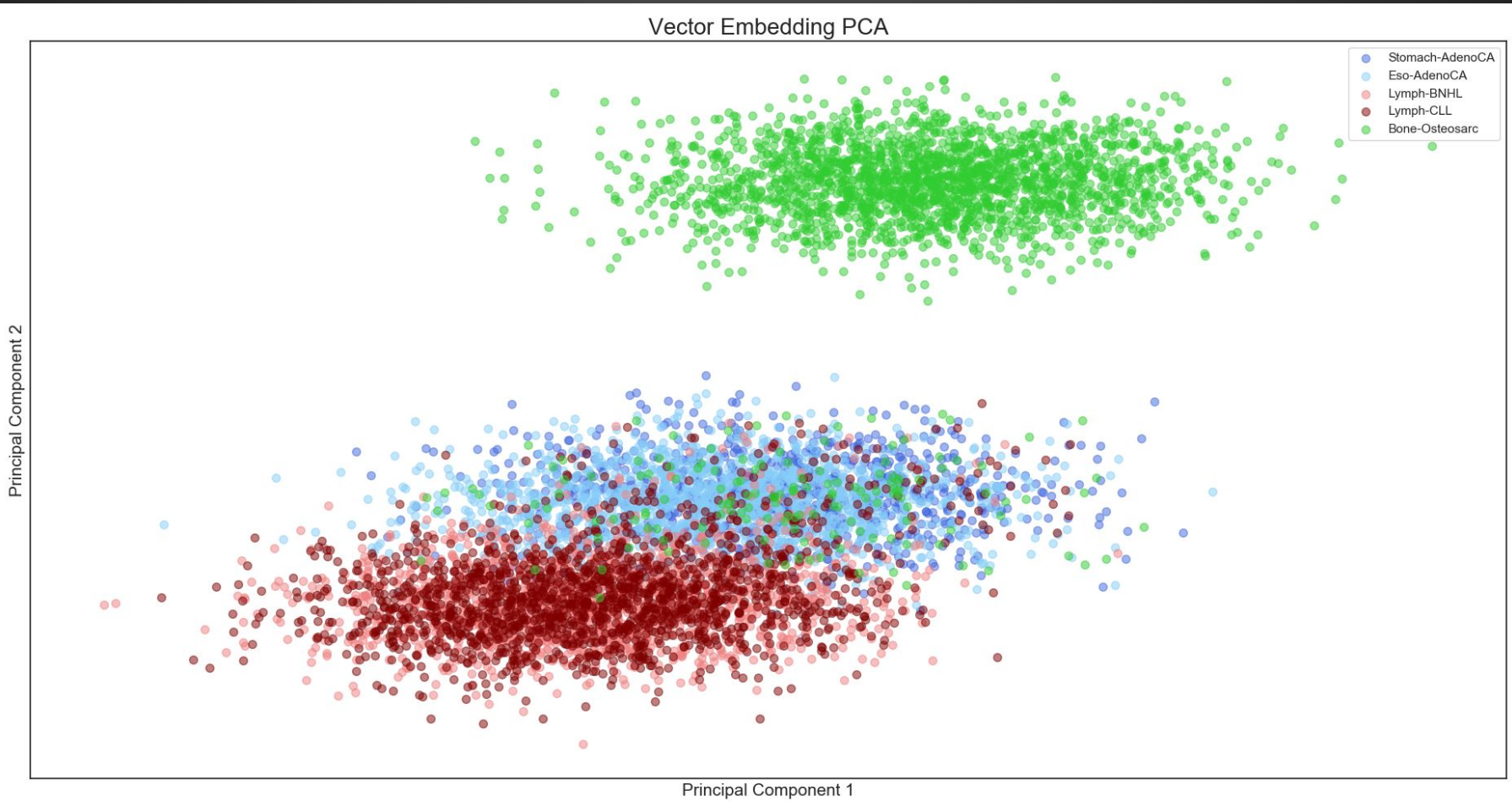
https://egg2.wustl.edu/roadmap/web_portal/chr_state_learning.html

Vector Space Embedding: *We want to control for Suppressed Chromatin Markers*



Vector Space Embedding: *I want to see what this looks like ...*




Vector Embedding PCA
Stomach-AdenoCA
Eso-AdenoCA
Lymph-BNHL
Lymph-CLL
Bone-Osteosarc
Principal Component 2
Principal Component 1

Conclusions

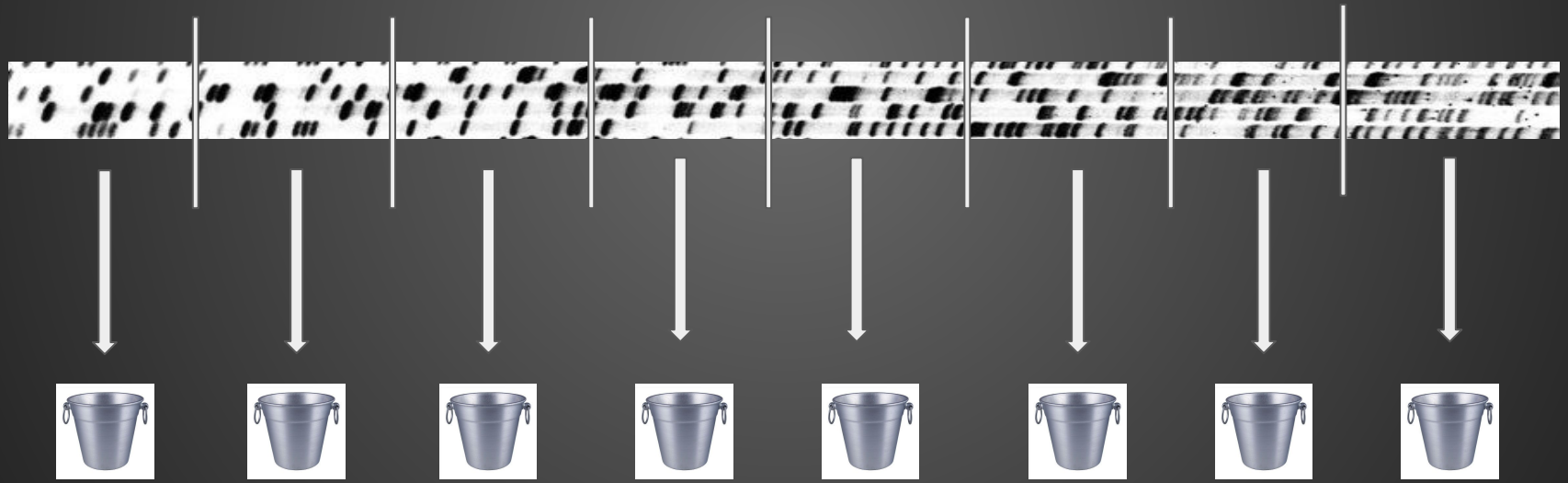
- Driver gene and pathway features don’t provide additional information for cancer classification. Training with mutation distribution and type is sufficient.
- Model misclassifications reflect shared biological characteristics in mutation topology.
- Discovered patterns in chromatin marks in misclassified cancers
- Research is fun
- I learned a lot of biology

Next Steps

Better genome segmentation

- Explore genome segmentations based on mutational process activity
- increase information content between mutational density and cell type

Naive Segmentation



Next Steps

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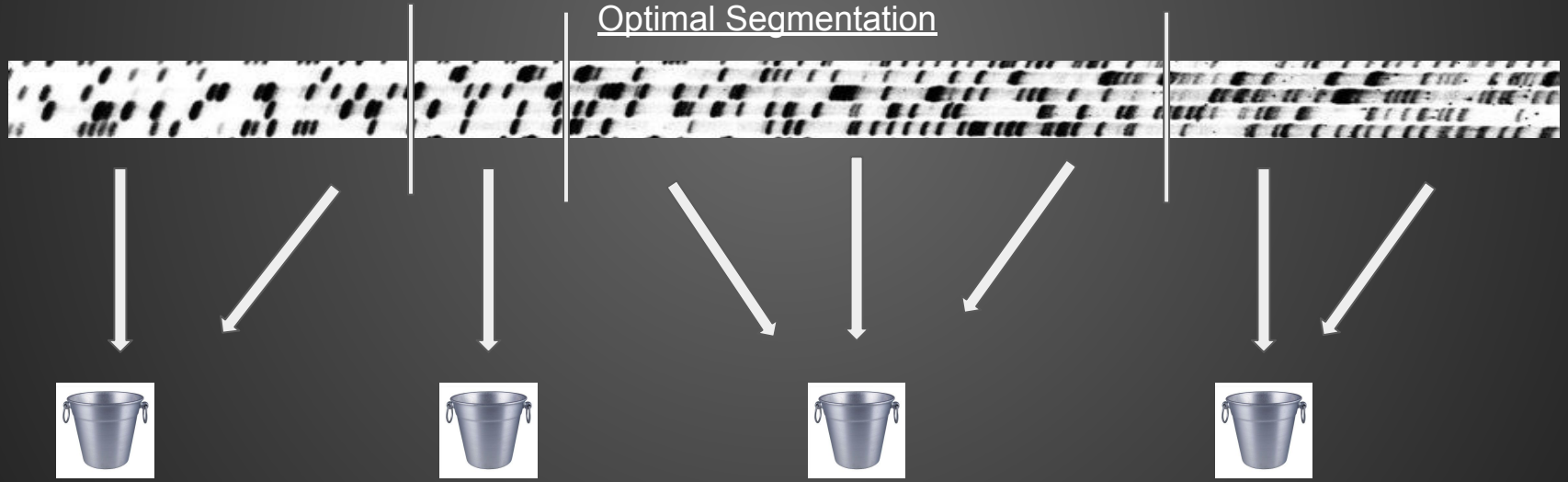
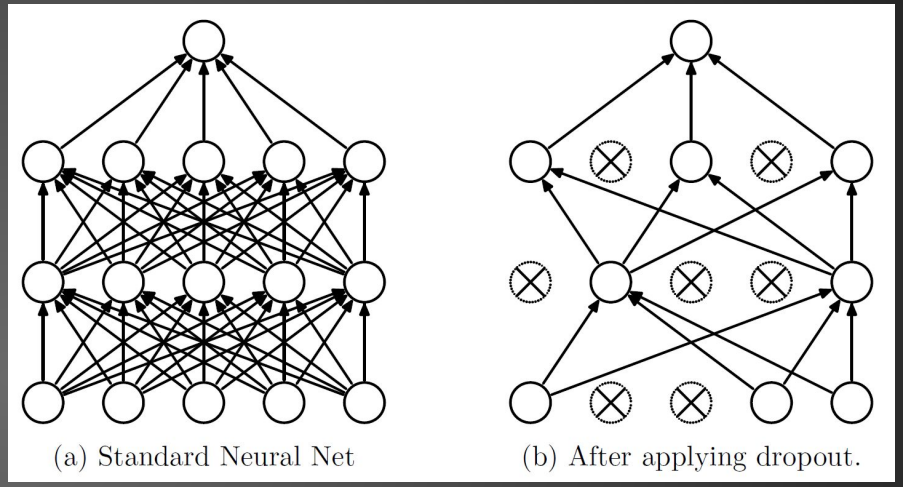
Optimal Segmentation



Next Steps

Extend classifier to rare cancer types

- Adopt a bayesian approach by implementing MC- dropout
- Certainty Estimates provide interpretable results

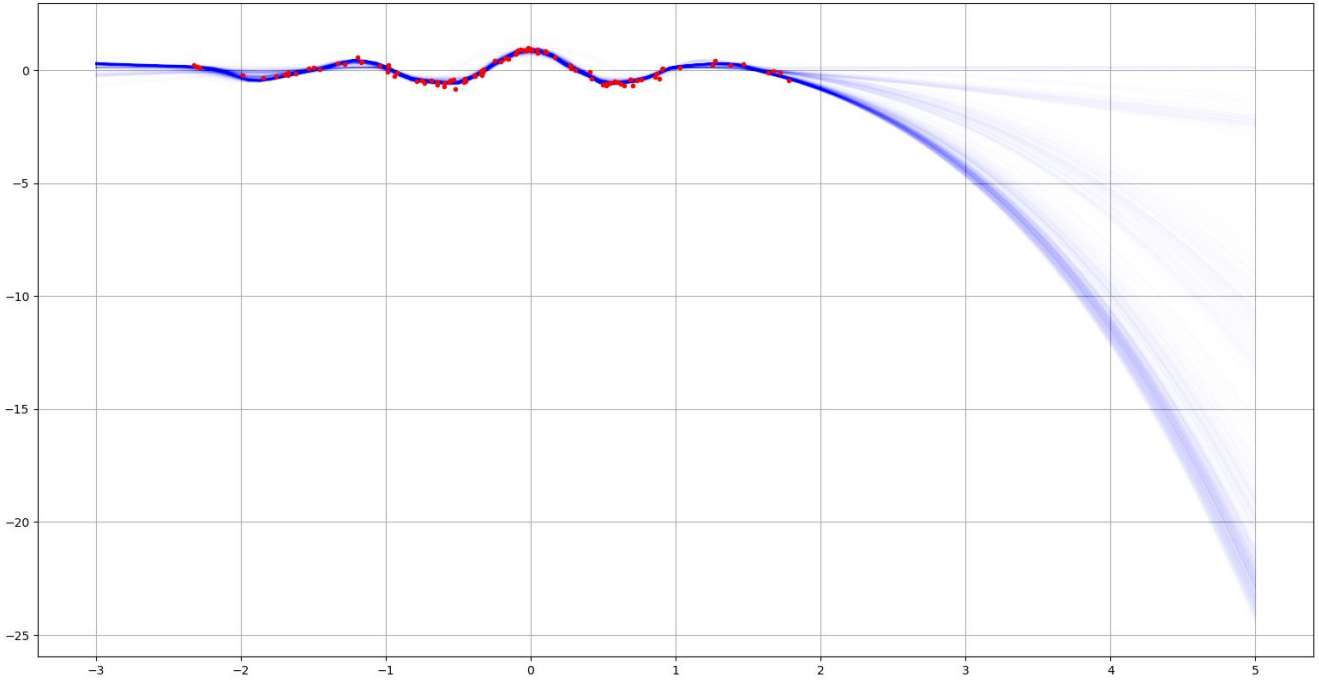


Source: Srivastava, Hinton, Krizhevsky, Sutskever and Salakhutdinov (2014)

MC-dropout (Monte Carlo Dropout)*: dropping neuron activations during test time ~ Non-deterministic*

- Generates predictions that one can interpret as samples from a probability distribution

Regression Example



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