W207.6 Final Project - Predicting Cancer Type from Tumor Mutations

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Overview

In this project, we analyze the tumor mutation dataset from PanCancer Atlas Initiative https://www.cell.com/pb-assets/consortium/pancanceratlas/pancani3/index.html. This is a cancer dataset comprising over 10,000 patients diagnosed with cancer. Overall, the study collected diverse and detailed molecular information on each patient's tumor, including DNA sequencing.

Primary Dataset

The primary dataset we will be using is the somatic mutations file. In addition, we may pull some patient features like gender and age at diagnosis from the clinical patient file.

Number of Instances: 3,600,963 somatic mutations for 10,956 cancer patients Number of Attributes: ~100 attributes for mutations, ~700 clinical attributes for patients. We will aggregate the mutation data by gene for each patient, reducing the number of attributes by patient to ~ 500-1000 features.

Background

By comparing the DNA from normal tissue cells to those of the cancerous cells, somatic mutations can be identified and characterized. Somatic mutations are non-inherited variations to the DNA of a cell that arise during an individual's lifetime. We will use these DNA mutations to predict cancer type, classified into 33 different tissue/organ types.

Motivation

There is clinical value in being able to predict cancer type based on molecular profiles. For some patients diagnosed with cancer, the biopsied tumor doesn't match the histologic characteristics of the organ/tissue site. For example, a patient may have a liver tumor that cannot be characterized as liver cells when reviewed by the pathologist. In these cases, the cancer may have originated from another site and has metastasized to the liver. This is where genomic tumor data may provide insights by predicting the 'cell of origin', leading to a better-suited therapy for the patient.

```
import pandas as pd
import urllib.request
import numpy as np
import glob
import os
import warnings
from textwrap import wrap
import matplotlib.pyplot as plt
from IPython.display import display
import time
from IPython.core.interactiveshell import InteractiveShell
InteractiveShell.ast_node_interactivity = "all"

from sklearn import preprocessing
from sklearn.feature_selection import SelectKBest
from sklearn.feature_selection import chi2
from sklearn.feature_selection import RFE
from sklearn import preprocessing
from sklearn import metrics
from sklearn.metrics import precision_recall_fscore_support
from sklearn.metrics import accuracy_score
from sklearn.metrics import confusion_matrix
from sklearn.model_selection import train_test_split
from sklearn.decomposition import PCA
from sklearn.model_selection import StratifiedKFold
from sklearn.naive_bayes import MultinomialNB
from sklearn.neighbors import KNeighborsClassifier
from sklearn.linear_model import LogisticRegression
from sklearn.tree import DecisionTreeClassifier
from sklearn.ensemble import RandomForestClassifier
from sklearn.model_selection import GridSearchCV
from sklearn.svm import LinearSVC
from sklearn.svm import SVC
#import xgboost as xgb
import tensorflow as tf
import tensorflow.keras as K
from tensorflow.keras.layers import Dense as Dense
from tensorflow.keras.utils import to_categorical
from tensorflow.keras import regularizers
from tensorflow.keras.layers import Dropout

plt.rcParams.update({'figure.max_open_warning': 0})
```

```
from google.colab import drive
drive.mount('/content/drive')
```

```
Go to this URL in a browser: https://accounts.google.com/o/oauth2/auth?client_id=947318989803-6bn6qk8qdgf4n4g3pfee6491hc0brc4i.apps.googleuserconten

Enter your authorization code:
··········
Mounted at /content/drive
```

```
cd /content/drive/My Drive/berkeley/W207 machine learning/Final Project/w207_6_sum19_g5_final_project
```

```
/content/drive/My Drive/berkeley/W207 machine learning/Final Project/w207_6_sum19_g5_final_project
```

Data Collection

For our analysis of cancer prediction using gene mutation and clinical data from patients, we will gather data from multiple sources. First we obtain the somatic mutation data from the PanCancerAtlas website (https://gdc.cancer.gov/about-data/publications/pancanatlas). We also download the patient clinical data that corresponds to the tumor data. At this time, we are not bringing in clinical features, but as the project progresses, we would like to bring in a few features from this clinical dataset (e.g. age a diagnosis, gender). In our notebook, we store this data locally so that it does not have to be downloaded if the notebook kernel is restarted and run multiple times.

```
# to make this notebook's output stable across runs
np.random.seed(42)


# create the directory where the downloaded directory is stored
data_dir = "./data"
if not os.path.isdir(data_dir):
    os.makedirs(data_dir)
```

Download the somatic mutations file

This file is in the 'MAF' file format, a bioinformatics tab separated format that can contains one record for each mutation observed in a patient tumor sample.

```
# This downloads a 753 MB somatic mutations gzip file.
# This will take about 1-5 mins depending on your
# connection speed.
mutations_filename = "./data/somatic_mutations.maf.gz"
if os.path.isfile(mutations_filename):
    print("Skipping download, as file %s is present" %(mutations_filename))
else:
    print('Downloading mutation data. 753 MB (may take a few minutes)...')
    url = 'http://api.gdc.cancer.gov/data/1c8cfe5f-e52d-41ba-94da-f15ea1337efc'
    urllib.request.urlretrieve(url, mutations_filename)
print("done.")
```

```
Skipping download, as file ./data/somatic_mutations.maf.gz is present
done.
```

Download the patient clinical data

```
# This downloads an 18 MB patient clinical data file
patient_filename = "./data/patient_clinical_data.txt"
if os.path.isfile(patient_filename):
    print("Skipping download, as file %s is present" %(patient_filename))
else:
    print('Downloading clinical data ...')
    url = 'http://api.gdc.cancer.gov/data/0fc78496-818b-4896-bd83-52db1f533c5c'
    urllib.request.urlretrieve(url, patient_filename)
print("done.")
```

```
Skipping download, as file ./data/patient_clinical_data.txt is present
done.
```

The data dictionary

All data source files are downloaded above. This dataset, is a data dictionary that will allow us to translate cancer type codes to cancer type names.

```
# This loads the data dictionary to will convert
# the tumor_sample_barcode into a cancer_type
# and provide full names for the cancer types
tcga_dict = open("./tcga_dictionaries.txt","r")
dict_name_index = 0 #Set dictionary index counter to 0
for line in tcga_dict:
    if line.startswith("#"): #If line starts with #, the next line will be a known dictionary
        dict_name_index += 1
    elif dict_name_index == 4:
        tissue_source_site = eval(line)
    elif dict_name_index == 5:
        code_to_disease = eval(line)
    elif dict_name_index == 6:
        disease_to_code = eval(line)
```

Loading Gene Mutation Data

Here we read the gene mutation data. This data file contains many columns, but after careful curation, we have decided to consider the following colums:

1. **tumor_sample_barcode**: this contains the barcode with the first 12 characters identifying the patient
2. **gene**: this is the actual gene that has been mutated (for e.g. TACC2, JAKMIP3, PANX3)
3. **gene_type**: this indicates if the gene is protein coding or not.
4. **chromosome start end Strand**: the chromosome, start position and end position tells us the location of the gene where the mutation is seen. Strand indicates if it is on the forward or reverse strand of the DNA.
5. **variant_type**: this indicates if it is a single substitution mutation (SNP), a small deletion (DEL), or small insertion (INS), two nucleotide substitution (DNP), three nucleotide substitution (TNP), or more that three nucleotide substitution (ONP)
6. **variant_classification**: this indicates what kind of molecular effect that this mutation will have on the protein. The most common classes indicate if the substitution causes a change to the amino acid (missense vs silent). Nonsense mutations cause premature termination of the protein; frameshift mutations cause a misreading of the amino acid sequence.
7. **variant_impact**: this indicates how damaging the mutation -- HIGH, MODERATE, MODIFIER, or LOW.

```
# Load the mutations dataframe
print('Loading mutations dataframe ...')

mutations = pd.read_csv(mutations_filename, compression='gzip',
                        sep='\t',
                        usecols=['Tumor_Sample_Barcode','Hugo_Symbol', 'BIOTYPE',
                                 'Chromosome', 'Start_Position',  'End_Position', 'Strand',
                                 'Variant_Type',  'Variant_Classification', 'IMPACT' ])

print("done.")

# Set mutations index
mutations['row'] = np.arange(len(mutations))
mutations.set_index('row', inplace=True)

# Rename the columns to more consistent names
renamed_columns = { 'Tumor_Sample_Barcode': 'tumor_sample_barcode',
                    'Hugo_Symbol': 'gene',
                    'BIOTYPE': 'gene_type',
                    'Chromosome': 'chromosome',
                    'Start_Position': 'start',
                    'End_Position': 'end',
                    'Strand': 'strand',
                    'Variant_Type': 'variant_type',
                    'Variant_Classification': 'variant_classification',
                    'IMPACT': 'variant_impact'}
mutations.rename(renamed_columns, inplace=True, axis=1)


print("\nMutations count:       ", mutations.tumor_sample_barcode.count())
print("Number of unique samples:", mutations.tumor_sample_barcode.nunique())
mutations.head(5)
```

```
Loading mutations dataframe ...
/usr/local/lib/python3.6/dist-packages/IPython/core/interactiveshell.py:2718: DtypeWarning: Columns (4) have mixed types. Specify dtype option on imp
  interactivity=interactivity, compiler=compiler, result=result)
done.

Mutations count:        3600963
Number of unique samples: 10295
```

row	gene	chromosome	start	end	strand	variant_classification	variant_type	tumor_sample_barcode	gene_type	variant_impact
0	TACC2	10	123810032	123810032	+	Missense_Mutation	SNP	TCGA-02-0003-01A-01D-1490-08	protein_coding	MODERATE
1	JAKMIP3	10	133967449	133967449	+	Silent	SNP	TCGA-02-0003-01A-01D-1490-08	protein_coding	LOW
2	PANX3	11	124489539	124489539	+	Missense_Mutation	SNP	TCGA-02-0003-01A-01D-1490-08	protein_coding	MODERATE
3	SPI1	11	47380512	47380512	+	Missense_Mutation	SNP	TCGA-02-0003-01A-01D-1490-08	protein_coding	MODERATE
4	NAALAD2	11	89868837	89868837	+	Missense_Mutation	SNP	TCGA-02-0003-01A-01D-1490-08	protein_coding	MODERATE

The actual cancer type can be found by parsing the tumor sample barcode and then looking up the cancer type code in the dictionary based on the tissue source site portion of the tumor sample barcode

```
# Parse the tissue source site from the tumor sample barcode.  Then use the
# tissue site source to lookup the cancer type from the tcga_dictionaries
def parse_cancer_type(tumor_sample_barcode):
    tss = tumor_sample_barcode.split("-")[1] #Extra the tissue source site from the tcga_id
    cancer_type = disease_to_code[tissue_source_site[tss][1]][0] #Convert from tss to disease to code
    return cancer_type


mutations['cancer_type'] = mutations['tumor_sample_barcode'].apply(parse_cancer_type)
print("Number of unique cancer types:", mutations.cancer_type.nunique())
```

```
Number of unique cancer types: 33
```

Loading Patient Data

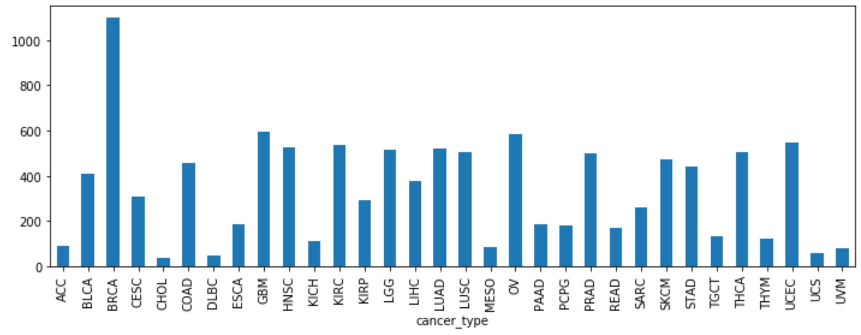
Here we load the clinical data. This is data for patients for whom we collected the gene mutation data above. The patients are identified by $patient\_barcode$. We will use this field to populate the gene mutation data from the dataframe above in the table we are about to read. The clinical data has patient information such as gender and age at diagnosis.

```
# Load the clinical data
print('Loading clinical dataframe ...')
clinical = pd.read_csv(patient_filename, sep='\t',
                        usecols=['bcr_patient_barcode', 'acronym', 'gender',
                                 'age_at_initial_pathologic_diagnosis'])

# Rename the columns to more consistent names
renamed_columns = { 'bcr_patient_barcode': 'patient_barcode',
                    'acronym': 'cancer_type' }
clinical.rename(renamed_columns, inplace=True, axis=1)

print('Clinical count', clinical.patient_barcode.count())
display(clinical.head(5))

# Get cancer types
cancer_types = clinical['cancer_type'].unique()
print("\nNumber of cancer types", len(cancer_types))

# Get number of cases per cancer type
group_by_patient = clinical.groupby(['cancer_type'])['patient_barcode'].nunique()
print("Number of patients", group_by_patient.sum())
group_by_patient.plot.bar(figsize=(12,4))
```

```
Loading clinical dataframe ...
Clinical count 10956
/usr/local/lib/python3.6/dist-packages/IPython/core/interactiveshell.py:2718: DtypeWarning: Columns (9) have mixed types. Specify dtype option on im
  interactivity=interactivity, compiler=compiler, result=result)
```

	patient_barcode	cancer_type	gender	age_at_initial_pathologic_diagnosis
0	TCGA-OR-A5J1	ACC	MALE	58
1	TCGA-OR-A5J2	ACC	FEMALE	44
2	TCGA-OR-A5J3	ACC	FEMALE	23
3	TCGA-OR-A5J4	ACC	FEMALE	23
4	TCGA-OR-A5J5	ACC	MALE	30

```
Number of cancer types 32
Number of patients 10956
<matplotlib.axes._subplots.AxesSubplot at 0x7fbdffd18780>
```



Creating Merged Data

Now that we have both gene and cancer data in one dataframe, and the patient clinical data in another dataframe, we will use the **patient_barcode** to merge these into a single table. With this, we can drop the tumor_sample_barcode column, since it has served its purpose. Looking at the data, it seems like some patient data is missing from the gene data. Simultaneously, some data in the gene dataframe does not have corresponding clinical data. Hence our merged dataframe size will be lower than the original mutations dataframe size.

```
# Get the patient barcode.  This is what we will use to join the mutations to the clinical data
def parse_patient_barcode(tumor_sample_barcode):
        return tumor_sample_barcode[0:12]


mutations['patient_barcode'] = mutations['tumor_sample_barcode'].apply(parse_patient_barcode)
mutations = mutations.drop(['tumor_sample_barcode'], axis=1)
mutations = mutations.drop(['cancer_type'], axis=1)
print("Number of unique patients:", mutations['patient_barcode'].nunique())
```

```
Number of unique patients: 10224
```

```
clinical['patient_barcode'].isnull().values.any()
```

```
False
```

```
missing_count = 0
gene_barcode_set = set(mutations.patient_barcode.unique())
for bc in gene_barcode_set:
    if bc not in set(clinical.patient_barcode.unique()):
        missing_count += 1
print("%d patients with gene data missing in clinical data" %missing_count)
```

```
216 patients with gene data missing in clinical data
```

```
merged = mutations.merge(clinical, left_on='patient_barcode', right_on='patient_barcode')
print('Merged mutations count:    ', merged.patient_barcode.count())
print('Number of unique patients:', merged.patient_barcode.nunique())
print('Number of cancer types:    ', merged.cancer_type.nunique())
```

```
Merged mutations count:     3570876
Number of unique patients: 10008
Number of cancer types:     32
```

Eliminate non-coding genes.

This is a common filter in bioinformatics analysis, eliminating genes that do not code for proteins.

```
# Eliminate non-coding genes
def eliminate_non_coding_genes(data):
    data                          = data[data.gene_type == 'protein_coding']
    return data

before_count               = merged.gene.nunique()
merged = eliminate_non_coding_genes(merged)
after_count                = merged.gene.nunique()
print("Filtered out ", str(before_count -after_count), "genes")
```

```
Filtered out  2113 genes
```

Split the data into training and test datasets

Split the data into a training and test split. We will use a split of 80% training, 20% test.
We will split based on the patient_barcode. As part of feature engineering, we will be aggregating mutations, so that each example will be represented as a patient (tumor), with columns for each gene.

```
#
# Split the patients into training and test
#
def split_patient_data():
    patient_data = merged.patient_barcode.unique()

    le      = preprocessing.LabelEncoder()
    patient_labels_string = merged.groupby('patient_barcode')['cancer_type'].nunique()
    patient_labels = le.fit_transform(patient_labels_string)

    print("Number of unique patients:           ", patient_data.shape[0])
    print("Number of labels for unique patients:", len(patient_labels))

    train_data, test_data, train_labels, test_labels = train_test_split(
                                                           patient_data, patient_labels,
                                                           stratify=patient_labels,
                                                           test_size=0.20)



    print("\ntraining patients:  ", train_data.shape[0])
    print("test patients:      ", test_data.shape[0])
    return {'train_patients': train_data, 'test_patients': test_data}


#
#  Split Mutations data (based on patient split) and
#  write out data files
#
def split_and_save_mutation_data():
    split = split_patient_data()
    train_patients = split['train_patients']
    test_patients  = split['test_patients']

    train_mutations = merged[merged.patient_barcode.isin(train_patients)]
    test_mutations  = merged[merged.patient_barcode.isin(test_patients)]
    print("\ntraining data:      ", train_mutations.shape[0])
    print("test data:          ", test_mutations.shape[0])
    print("\nall data:           ", merged.shape[0])
    print("train + test:       ", train_mutations.shape[0] + test_mutations.shape[0])

    # Write out mutations training data as csv file
    print("\nWriting training set ...")
    train_mutations.to_csv("./data/somatic_mutations_train.csv")
    print("done.")

    # Write out mutations test data as csv file
    print("\nWriting test set ...")
    test_mutations.to_csv("./data/somatic_mutations_test.csv")
    print("done.")

split_and_save_mutation_data()
```

```
Number of unique patients:            10008
Number of labels for unique patients: 10008

training patients:   8006
test patients:       2002

training data:       2856316
test data:           632127

all data:            3488443
train + test:        3488443

Writing training set ...
done.

Writing test set ...
done.
```

EDA and Feature Selection

```
# Remove old features_ files
#filenames = glob.glob('./data/features_*.csv')

# Iterate over the list of filepaths & remove each file.
#for filePath in filenames:
#    try:
#        os.remove(filePath)
#    except OSError:
#        print("Error while deleting file")
```

Here, we open the data we put together in the previous notebook. For the first analysis, we look at $cancer\_type$, $patient\_barcode$, $gene$ and $gene_type$.

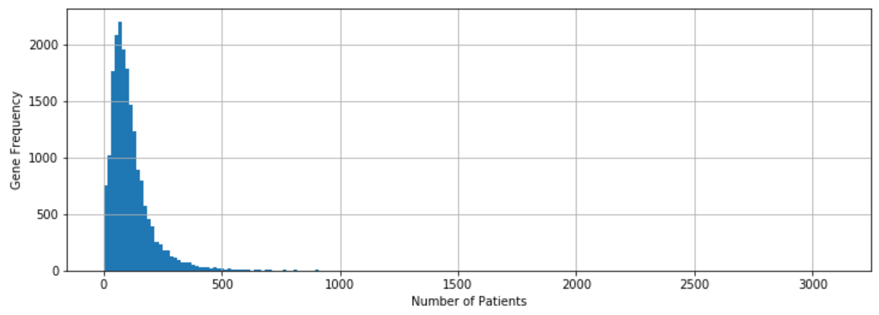
```
print('Loading data ...')
mutations = {}
mutations['train'] = pd.read_csv("./data/somatic_mutations_train.csv",
                             usecols=['cancer_type', 'patient_barcode', 'gene', 'gene_type'])
mutations['test']  = pd.read_csv("./data/somatic_mutations_test.csv",
                             usecols=['cancer_type', 'patient_barcode', 'gene', 'gene_type'])
print("done.")
print("Mutations training data count:", mutations['train']['patient_barcode'].count())
print("Mutations test data count:     ", mutations['test']['patient_barcode'].count())
```

```
Loading data ...
done.
Mutations training data count: 2856316
Mutations test data count:     632127
```

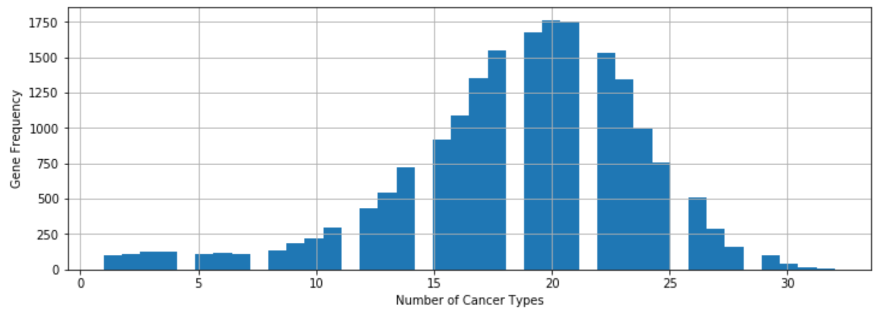
Show distribution of genes across patient tumors

```
# Show the distribution of genes across patient tumors
gene_count          = mutations['train'].groupby(['gene'])['patient_barcode'].nunique().reset_index(name='count')
gene_count.columns = ['gene', 'patient_count']
gene_count          = gene_count.sort_values(['patient_count', 'gene'], ascending=[0,1])
print('Genes by patient frequency')
print("  mean:", int(gene_count['patient_count'].mean()))
print("  min: ", int(gene_count['patient_count'].min()))
print("  max: ", int(gene_count['patient_count'].max()))

ax = gene_count['patient_count'].hist(bins=200, figsize=(12,4))
ax.set_xlabel("Number of Patients")
ax.set_ylabel("Gene Frequency")
plt.show()

gene_cc_count          = mutations['train'].groupby(['gene'])['cancer_type'].nunique().reset_index(name='count')
gene_cc_count.columns = ['gene', 'cancer_type_count']
gene_cc_count          = gene_cc_count.sort_values(['cancer_type_count', 'gene'], ascending=[0,1])
print('\nGenes by cancer type frequency')
print("  mean:", int(gene_cc_count['cancer_type_count'].mean()))
print("  min: ", int(gene_cc_count['cancer_type_count'].min()))
print("  max: ", int(gene_cc_count['cancer_type_count'].max()))


ax = gene_cc_count['cancer_type_count'].hist(bins=40, figsize=(12,4))
ax.set_xlabel("Number of Cancer Types")
ax.set_ylabel("Gene Frequency")
plt.show()
```

```
Genes by patient frequency
  mean: 114
  min:  1
  max:  3093
Text(0.5, 0, 'Number of Patients')Text(0, 0.5, 'Gene Frequency')
```



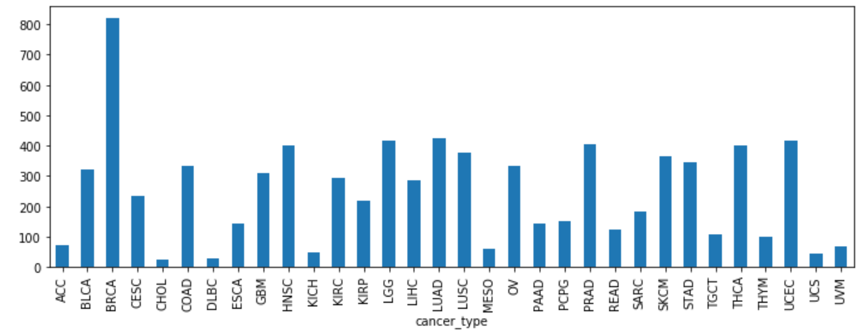
```
Genes by cancer type frequency
  mean: 18
  min:  1
  max:  32
Text(0.5, 0, 'Number of Cancer Types')Text(0, 0.5, 'Gene Frequency')
```



From the histogram above, it is clear that even through we have a large number of genes, only a small number of them are turned on in the patient tumor data that we have. This is the classic problem of a large feature space with a much smaller number of samples. Hence we will need to perform a dimensionality reduction technique such as PCA here.

```
# Print out the number of cancer types that are present in the
# mutations dataset
cancer_types = mutations['train'].cancer_type.unique()
print("\nNumber of cancer types:", len(cancer_types))

# Get number of cases per cancer type
group_patients_by_cancer = mutations['train'].groupby(['cancer_type'])['patient_barcode'].nunique()
print("\nNumber of patients:", group_patients_by_cancer.sum())
group_patients_by_cancer.plot.bar(figsize=(12,4))
```

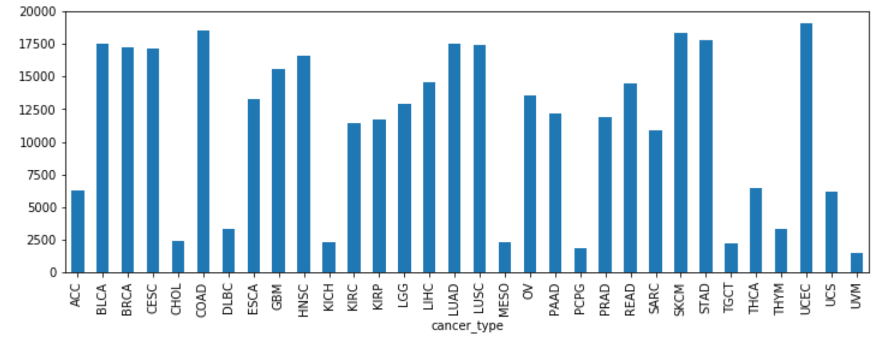
```
Number of cancer types: 32

Number of patients: 8006
<matplotlib.axes._subplots.AxesSubplot at 0x7fbdecf07b00>
```



The above chart shows that there are some cancers, such as BRCA and LUAD that have a large representation in our dataset, but other such as DBLC and UCS that are present in much smaller numbers. This will present a challenge for our classifier. Specifically, we want our classifier to be able to classify each of the 32 types of cancers with high precision, but the model should also be able to identify the cancers that don't have a proportionate representation in our data set. It could be that these are cancers are rare, or perhaps they are simply rare in our dataset. **Note:** add more details about the cancers that are abundant as well as rare in this dataset.

```python
# Get the unique genes per cancer type
group_genes_by_cancer = mutations['train'].groupby(['cancer_type'])['gene'].nunique();
group_genes_by_cancer.plot.bar(figsize=(12,4))
print("Mean number of genes represented for each cancer type:", int(np.round(group_genes_by_cancer.mean())))
print("Min number of genes represented for each cancer type: ", int(np.round(group_genes_by_cancer.min())))
print("Max number of genes represented for each cancer type: ", int(np.round(group_genes_by_cancer.max())))
```

```
<matplotlib.axes._subplots.AxesSubplot at 0x7fbdec673d68>Mean number of genes represented for each cancer type: 11173
Min number of genes represented for each cancer type:  1452
Max number of genes represented for each cancer type:  19069
```



The above bar chart gives us an idea of how many genes (features for us) are *on* for each of the cancer types. Cross referencing this chart with the previous one, we see that for some cancers such as DLBC and UCS we have a fair number of active features, even though the number of cases of such cancers are low. We should be able to person isolated (one-vs-rest) analysis for these cases. However, for other cancers, such as KICH (Kidney Chromophobe) and UVM (Uveal Melanoma) we have both a low occurance rate, and a low number of active features. This second category of cancers will need to be handled with care.

Functions for feature engineering

```python
# Create feature matrix each row is a patient tumor; each column is a gene
def create_patient_x_gene_matrix(mutations, feature_genes, description, save=True):
    cases = list()
    grouped = mutations.groupby('patient_barcode')
    i = int(0)

    cols = ['case_id', 'cancer_type']
    for gene in feature_genes:
        cols.append(gene)


    for name, group in grouped:
        case = list()
        case.append(name)
        for cc in group.cancer_type.head(1):
            case.append(cc)

        for gene_flag in feature_genes.isin(group.gene.unique()):
            switch = 0
            if gene_flag == True:
                switch = 1
            case.append(switch)
        cases.append(case)


    cases_df = pd.DataFrame(cases)
    cases_df.columns = cols
    print("  ", cases_df.shape)

    # Write out transformed data to csv
    if save:
        fileName = "./data/" + description + ".csv"
        print("  writing", fileName, "...")
        cases_df.to_csv(fileName)
        print("  done.")

    return cases_df
```

```python
def show_genes_across_cancer_types(top_gene_cancer_matrix, top_n_gene_count, total_gene_count):
    plt.rcParams["figure.figsize"] = (10,4)
    sums_by_cancer_type = top_gene_cancer_matrix.sum(axis=1, skipna=True, numeric_only=True)
    sorted = sums_by_cancer_type.sort_values(ascending=False).reindex()
    df = pd.DataFrame(sorted).reset_index()
    df.columns = ['gene', 'patient_count']
    df.reset_index()
    title = 'Patient counts for genes (top ' + str(top_n_gene_count) + ')';
    ax = df.head(50).plot.bar(x='gene', y='patient_count', legend=None, title=title)

    cancer_type_present_count = top_gene_cancer_matrix.astype(bool).sum(axis=1, skipna=True, numeric_only=True)
    sorted = cancer_type_present_count.sort_values(ascending=False).reindex()
    df = pd.DataFrame(sorted).reset_index()
    df.columns = ['gene', 'present_in_cancer_type_count']
    df.reset_index()

    axarr = df.hist(bins=32)

    for ax in axarr.flatten():
        ax.set_xlabel("Number of cancer types gene is present")
        ax.set_ylabel("Gene frequency")

    return df



def create_feature_matrix(mutations_train, mutations_test, top_n_gene_count, save, description, charts=True):
    print("Formatting gene matrix with top ", top_n_gene_count, "genes from each cancer type")

    # Now try to find the most common genes per cancer type and
    # merge these together to come up with a master list
    cancer_gene_count = mutations_train.groupby(['cancer_type', 'gene'])['patient_barcode'].nunique().reset_index(name='count')
    cancer_gene_count.columns = ['cancer_type', 'gene', 'patient_count']



    # Now create a large matrix, row is the gene, column for each cancer type
    df = pd.DataFrame(cancer_gene_count, columns=['cancer_type', 'gene', 'patient_count'])
    gene_cancer_matrix = pd.pivot_table(df, values='patient_count', index=['gene'],
                         columns=['cancer_type'], aggfunc=np.sum, fill_value=0)



    # Now find the top n genes for each cancer type
    top_genes = []
    idx = 0

    plt.rcParams["figure.figsize"] = (20,20)
    for cancer_type in gene_cancer_matrix.columns:
        sorted_genes = gene_cancer_matrix[cancer_type].sort_values(ascending=False)
        top_rows = sorted_genes[sorted_genes > 0].head(top_n_gene_count)
        for gene, patient_count in top_rows.items():
            top_genes.append(list([cancer_type, gene, patient_count]))


    # Turn this back into a matrix, row is gene, column for each cancer type
    top_df = pd.DataFrame(top_genes, columns=['cancer_type', 'gene', 'patient_count'])
    top_gene_cancer_matrix = pd.pivot_table(top_df, values='patient_count', index=['gene'],
                         columns=['cancer_type'], aggfunc=np.sum, fill_value=0)
    print("  number of genes:", top_gene_cancer_matrix.shape[0])
    if charts:
        show_genes_across_cancer_types(top_gene_cancer_matrix,
                                   top_n_gene_count,
                                   top_gene_cancer_matrix.shape[0] )
    feature_genes = top_gene_cancer_matrix.index
    print("  number of genes after filter:", len(feature_genes))
    create_patient_x_gene_matrix(mutations_train, feature_genes, description + ".train", save)
    create_patient_x_gene_matrix(mutations_test,  feature_genes, description + ".test", save)


def create_best_fit_feature_matrix(mutations_train, mutations_test, top_n_genes, n_features,
                               save, description, charts=True):
    print("Formatting gene matrix with best fit for", n_features, "features")

    # Now try to find the most common genes per cancer type and
    # merge these together to come up with a master list
    cancer_gene_count = mutations_train.groupby(['cancer_type', 'gene'])['patient_barcode'].nunique().reset_index(name='count')
    cancer_gene_count.columns = ['cancer_type', 'gene', 'patient_count']



    # Now create a large matrix, row is the gene, column for each cancer type
    df = pd.DataFrame(cancer_gene_count, columns=['cancer_type', 'gene', 'patient_count'])
    gene_cancer_matrix = pd.pivot_table(df, values='patient_count', index=['gene'],
                         columns=['cancer_type'], aggfunc=np.sum, fill_value=0)



    # Now find the top n genes for each cancer type
    top_genes = []
    for cancer_type in gene_cancer_matrix.columns:
        sorted_genes = gene_cancer_matrix[cancer_type].sort_values(ascending=False)
        if (top_n_genes == None):
            top_rows = sorted_genes[sorted_genes > 0].head(top_n_genes)
        else:
            top_rows = sorted_genes
        for gene, patient_count in top_rows.items():
            top_genes.append(list([cancer_type, gene, patient_count]))


    # Turn this back into a matrix, row is patient, column for each gene
    top_df = pd.DataFrame(top_genes, columns=['cancer_type', 'gene', 'patient_count'])
    top_gene_cancer_matrix = pd.pivot_table(top_df, values='patient_count', index=['gene'],
                         columns=['cancer_type'], aggfunc=np.sum, fill_value=0)
    show_genes_across_cancer_types(top_gene_cancer_matrix,
                               top_n_genes,
                               n_features )

    #
    # Create feature matrix, each row is patient, columns are genes
    #
    feature_genes = top_gene_cancer_matrix.index
    print("  number of genes before best fit:     ", len(feature_genes))
    feature_matrix_train = create_patient_x_gene_matrix(mutations_train, feature_genes, '', False)
    feature_matrix_test  = create_patient_x_gene_matrix(mutations_test, feature_genes, '', False)

    #
    #  Try BestFit (chi squared test) to find most
    #  important genes
    #
    best_genes  = get_best_fit_features(feature_matrix_train, n_features)
    cancer_type = feature_matrix_train['cancer_type']
    case_id     = feature_matrix_train['case_id']
    data_train  = feature_matrix_train.loc[:, feature_matrix_train.columns.isin(best_genes)]

    print("  number of genes before after best fit:", data_train.shape[1])
    final_feature_matrix_train = pd.concat([case_id, cancer_type, data_train], axis=1)

    cancer_type = feature_matrix_test['cancer_type']
    case_id     = feature_matrix_test['case_id']
    data_test   = feature_matrix_test.loc[:, feature_matrix_test.columns.isin(best_genes)]
    final_feature_matrix_test = pd.concat([case_id, cancer_type, data_test], axis=1)

    if save:
        fileName = "./data/" + description  + ".train.csv"
        print("  writing", fileName, "...")
        print(" ", final_feature_matrix_train.shape)
        final_feature_matrix_train.to_csv(fileName)
        print("  done.")

        fileName = "./data/" + description  + ".test.csv"
        print("  writing", fileName, "...")
        print(" ", final_feature_matrix_test.shape)
        final_feature_matrix_test.to_csv(fileName)
        print("  done.")
```

```python
def get_best_fit_features(feature_matrix, n_features):
    #apply SelectKBest class to extract top n best features
    bestfeatures = SelectKBest(score_func=chi2, k=n_features)

    data = feature_matrix.loc[:, (feature_matrix.columns != 'cancer_type') & (feature_matrix.columns != 'case_id')]
    labels_string = feature_matrix['cancer_type']

    le = preprocessing.LabelEncoder()
    labels = le.fit_transform(labels_string)

    fit = bestfeatures.fit(data,labels)
    dfscores = pd.DataFrame(fit.scores_)
    dfcolumns = pd.DataFrame(data.columns)

    #concat two dataframes for better visualization
    featureScores = pd.concat([dfcolumns,dfscores],axis=1)
    featureScores.columns = ['gene','score']
    display(featureScores.nlargest(10,'score'))
    return list(featureScores.nlargest(n_features,'score')['gene'])


def create_all_feature_matrix(mutations_train, mutations_test, save, description):
    print("Formatting gene matrix with for all features")
    #
    # Create feature matrix, each row is patient, columns are genes
    #
    feature_genes = pd.Series(mutations_train.gene.unique())
    feature_matrix_train = create_patient_x_gene_matrix(mutations_train, feature_genes, description + ".train", save)
    feature_matrix_test  = create_patient_x_gene_matrix(mutations_test,  feature_genes, description + ".test", save)
    return feature_matrix_train, feature_matrix_test
```

```python
def create_l1_feature_matrix(train_features, test_features, label_encoder, description, save):

    train_first_cols    = train_features[train_features.columns[:2]]
    train_data          = train_features[train_features.columns[3:]]
    train_labels        = label_encoder.fit_transform(train_features.cancer_type)

    test_first_cols    = test_features[test_features.columns[:2]]
    test_data          = test_features[test_features.columns[3:]]
    test_labels        = label_encoder.fit_transform(test_features.cancer_type)

    params = {'C':  [100, 10, 1, .5]}

    for c_param in reversed(params['C']):
        # Keep this random seed here to make comparison easier.
        np.random.seed(0)

        #
        # Perform Logistic Regression on different C values
        # using L1 regularization
        #
        l1 = LogisticRegression(penalty='l1', tol=.01,
                                solver="liblinear", multi_class="ovr",
                                max_iter=500, C=c_param)
        # Fit model
        l1.fit(train_data, train_labels)


        # Get the features with non-zero coefficients.  We will use
        # this list to reduce the features
        non_zero_sums = np.where(np.sum(l1.coef_, axis=0) != 0)
        names = np.array(list(train_data.columns))
        non_zero_genes = names[non_zero_sums]


        #
        # Reduce feature size, only keeping features with non-zero weights
        # found using l1 regularization
        #
        trimmed_train_data = train_data[non_zero_genes]
        trimmed_test_data  = test_data[non_zero_genes]

        final_features_train = pd.concat([train_first_cols, trimmed_train_data], axis=1)
        final_features_test =  pd.concat([test_first_cols, trimmed_test_data], axis=1)

        if save:
            fileName = "./data/" + description + "_c" + str(c_param) + ".train.csv"
            print("  writing", fileName, "...")
            print(" ", final_features_train.shape)
            final_features_train.to_csv(fileName)
            print("  done.")

            fileName = "./data/" + description + "_c" + str(c_param) + ".test.csv"
            print("  writing", fileName, "...")
            print(" ", final_features_test.shape)
            final_features_test.to_csv(fileName)
            print("  done.")
```

```
def create_rfe_feature_matrix(train_features, test_features, label_encoder, description, save):
    train_first_cols    = train_features[train_features.columns[:2]]
    train_data          = train_features[train_features.columns[3:]]
    train_labels        = label_encoder.fit_transform(train_features.cancer_type)

    test_first_cols    = test_features[test_features.columns[:2]]
    test_data          = test_features[test_features.columns[3:]]
    test_labels        = label_encoder.fit_transform(test_features.cancer_type)

    lr = LogisticRegression(penalty='l2', tol=.01, max_iter=150,
                            C=0.25,
                            solver="liblinear", multi_class="ovr")
    rfe = RFE(estimator=lr, n_features_to_select=800, step=1)
    rfe.fit(train_data, train_labels)
    ranking = rfe.ranking_
    print(ranking)
```

Create different feature sets

Top n genes most frequent in each cancer type

Create a feature matrix, getting the top n genes that are most frequent per label (cancer type). Merge these genes and create a feature matrix, one row per patient tumor, column for each merged gene

```
create_feature_matrix(mutations['train'], mutations['test'], 1000, True, 'features_topgenes_small')
```

Use KBestFit to find best features (genes)

Create a feature matrix, getting the top 1000 genes that are most frequent per label (cancer type). Merge these genes. Then use sklearn BestFit to find top 5000 genes. Feature matrix will have one row per patient tumor, column for each 'bestfit' gene

```
create_best_fit_feature_matrix(mutations['train'], mutations['test'], 1000, 5000, True,
                          'features_bestfit_with_topgenes')
```

Create a feature matrix, using sklearn BestFit to find top 5000 genes. Feature matrix will have one row per patient tumor, column for each 'bestfit' gene

```
create_best_fit_feature_matrix(mutations['train'], mutations['test'], None, 5000, True,
                           'features_bestfit_med')
```

Create a feature matrix, using sklearn BestFit to find top 8000 genes. Feature matrix will have one row per patient tumor, column for each 'bestfit' gene

```
create_best_fit_feature_matrix(mutations['train'], mutations['test'],None, 8000, True,
                           'features_bestfit_large')
```

Use all genes

Create a feature matrix, Feature matrix will have one row per patient tumor, column for every gene encountered in training data set.

```
feature_matrix_train, feature_matrix_test = create_all_feature_matrix(mutations['train'],
                                                                  mutations['test'], True, 'features_all')
```

Use Recursive Feature Elimination

```
#
# Trim the features using Recursive Feature Elimination
#
#label_encoder            = preprocessing.LabelEncoder()
#create_rfe_feature_matrix(feature_matrix_train, feature_matrix_test, label_encoder,
#                          'rfe_logit', True)
```

Use Logistic Regression with L1 regularization a different C values

Trim the features using Logistic Regression, L1 regularization

```
label_encoder            = preprocessing.LabelEncoder()
create_l1_feature_matrix(feature_matrix_train, feature_matrix_test, label_encoder,
           'features_l1reg', True)
```

Use PCA for dimensionality reduction

```
pca = PCA()
all_features_train = feature_matrix_train.drop(columns=['case_id', 'cancer_type'])
pca.fit(all_features_train)
ev = np.cumsum(pca.explained_variance_ratio_)
evcount = len(ev[ev<99.0])
print("Number of features that explain 99% of the variance: ", evcount)
pca = PCA(n_components=evcount)
pca.fit(all_features_train)
train_PCA = pca.transform(all_features_train)
all_features_test = feature_matrix_test.drop(columns=['case_id', 'cancer_type'])
test_PCA = pca.transform(all_features_test)
```

```
train_PCA_df = pd.DataFrame(train_PCA)
train_PCA_df['case_id'] = feature_matrix_train['case_id']
train_PCA_df['cancer_type'] = feature_matrix_train['cancer_type']

test_PCA_df = pd.DataFrame(test_PCA)
test_PCA_df['case_id'] = feature_matrix_test['case_id']
test_PCA_df['cancer_type'] = feature_matrix_test['cancer_type']
```