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T1 ________________	1920593	F1 ________________
T2 ________________		F2 ________________
T3 ________________	Problem Chosen	F3 ________________
T4 ________________	C	F4 ________________

2019
MCM/ICM
Summary Sheet

The Opioids Crisis

In order to set realistic and proper goals for the spread and characteristics of the reported synthetic opioid and heroin incidents (cases) in and between the five states and their counties over time, our team makes an analysis and prediction on the spread of the most opioid. Then, we propose three practical actions for the governors to meet these goals. Specifically,

For part I, we first explore the opioids information from four aspects-level of analgesia, degree of addiction, duration of efficacy and effective speed. Secondly,regarding population, economy, modernization and geography as influential factors, we study the similarities and differences in the spread of the opioids. Next, the linear regression model is developed to identify the possible locations where specific opioid use might have started in each of the five states.

For part II, it is universally acknowledged that the economic status is a great endogenous factor in all social activities. On one hand, when the economic level becomes higher, people's tolerance to pain will be replaced by money if possible. However, on the other hand, this approach is addictive in the incorrect way of using it. From a point of view in the circulation, although opioid is on the list of strictly regulated drugs, many people take risks to synthesize and illegally buy and sell opioids because of its high price and high profits.

For part III, combining Game Theory, we give the strategy to decease the crisis of the ahuse in opioids.

Finally, for the governors, we prepare a memo to introduce the opioids, the prediction on original area of spread of opioids and our recommended strategies for opioids crisis.

Contents

1 Introduction

1.1 Problem Background

With the economics and scientific technology developed nowadays, the abuse of the opioids is becoming more and more rampant. In the United States, the opioids spread in the counties and states either for the treatment or for recreational purposes is experiencing a national crisis.

Opioids are classified into opioid receptor agonists, partial agonists, and antagonists based on their different affinities and intrinsic activities on opioid receptors. The C-terminal to cysteine residue region of the opioid receptor is highly conserved, and it inhibits adenylate cyclase (AC) and reduces intracellular cyclic adenosine monophosphate (cAMP) content by binding to the G protein. Opioid receptors can also be directly coupled to the ion channel through the G protein, inhibiting the opening of the voltage-gated calcium channel in the presynaptic nerve terminals, increasing the conduction of potassium ions, causing hyperpolarization of the cell membrane, thereby reducing cell excitability . However, opioids can increase the excitability of certain neural pathways by blocking inhibitory interneurons.

Opioids are classified into three categories based on their source, natural opioid alkaloids, semi-synthetic opioid alkaloid derivatives, and fully synthetic opioids. Opioid receptor agonists are potent analgesics that represent the drug morphine and can also cause euphoria. Opioid receptors acting on the central nervous system, inhibiting the ascending and descending pathways of pain, selectively alleviating or relieving the feeling of pain and causing unpleasant emotional reactions. However, these drugs have varying degrees of tolerance, physical and mental dependence, and sudden withdrawal can cause severe withdrawal reactions. (Heroin, codeine, Hydromorphone, Oxymorphine, meperidine, fentanyl fentanyl, methadone) Partial agonists: buprenorphine, butorphanol, nalbuphine, dezocine, Opioid receptor antagonists can competitively block opioid receptors, representing naloxone and naltrexone, which are mainly used for the continuous treatment of acute poisoning and addiction of opioids.

Several major problems are discussed in this paper, which are:

- A mathematical model using interpolation and linear regression to describe the spread and characteristics of the reported synthetic opioid and heroin incidents in and between the five states and their counties over time
- Identifying possible locations where specific opioid use might have started in each of the five states.
- Including important in our model using socio-economic data provided.
- using combination of the drug-reported data and socio-economic data to give a proposal for the opioid crisis.

1.2 Literature Review

A literatrue[1] say something about this problem.Opioids are classified into three categories based on their source, natural opioid alkaloids, semi-synthetic opioid alkaloid derivatives, and fully synthetic opioids. Opioid receptor agonists are potent analgesics that represent the drug morphine and can also cause euphoria. Opioid receptors acting on the central nervous system, inhibiting the ascending and descending pathways of pain, selectively alleviating or relieving the feeling of pain and causing unpleasant emotional reactions. However, these drugs have varying degrees of tolerance, physical and mental dependence, and sudden withdrawal can cause severe withdrawal reactions. (Heroin, codeine, Hydromorphone, Oxymorphine, meperidine, fentanyl fentanyl, methadone) Partial agonists: buprenorphine, butorphanol, nalbuphine, dezocine, Opioid receptor antagonists can competitively block opioid receptors, representing naloxone and naltrexone, which are mainly used for the continuous treatment of acute poisoning and addiction of opioids.

1.3 Our work

We use spline interpolation to fill in the map and use linear regression model to predict the change of drug reports in each region which indicates the spread and characteristics of drugs. To improve our models, we use multiple variables to do the regression, considering many factors such as economy and polulation.

We search for the information of different kinds of opioids and try to connect the effection with the level of analgesia, degree of addiction, duration of efficacy and effective speed.

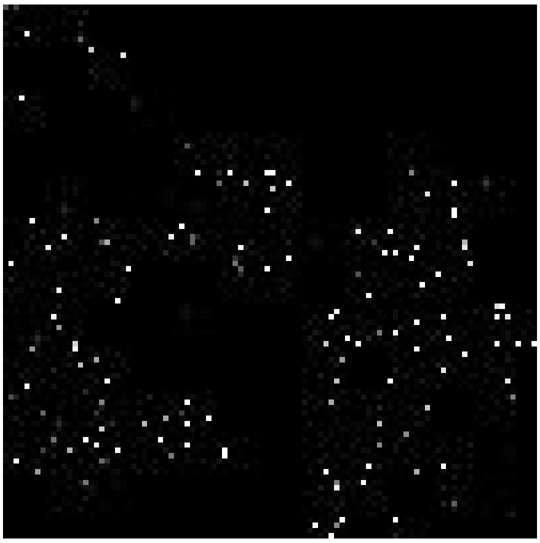
1. We do ...
2. We do ...
3. We do ...

2 Preparation of the Models

2.1 Assumptions

We firstly assume that each county has equal population and economical conditions and they are different merely in the name and position where they are. So we can see each county as a pixel in a BMP image with 'L' mode. That is to say, the drug-reported image is black and white and most pixel of the image is 0 i.e. black because they are not a county in the data.

As is illustrated in Fig.1, each county in the data is represented by a pixel and the brighter it is, the more reports of drug in this county which indicates the degree of severity.



(a) drug-reported map, 2010

(b) drug-reported map, 2017

Figure 1: the drug-reported map in several years made from NFLIS data. The brighter it is, the more reports of drug in this county.

2.2 Notations

The primary notations used in this paper are listed in **Table 1**.

Table 1: Notations

Symbol	Definition
$bright$	the brightness of the pixel (the drug reports of the county or the region)
$year$	the reported year

3 The Models

3.1 Analysis of Data

As is shown in Fig.2We can see that state PA is significantly higher in terms of drug report comparing to any other state. However, it is possible that PA has more counties than others, so we calculate average drug reports in one county of each state. In this case, we can see from Fig.3 that the state OH and PA share a high average drug reports in one county. This is obviously more convincing.

There are 69 different kinds of drugs in the data set but some drugs reported merely several times. We choose find the 10 most-reported drugs in Fig.4. Heroin ranks first whose reports exceeding 0.3 million.

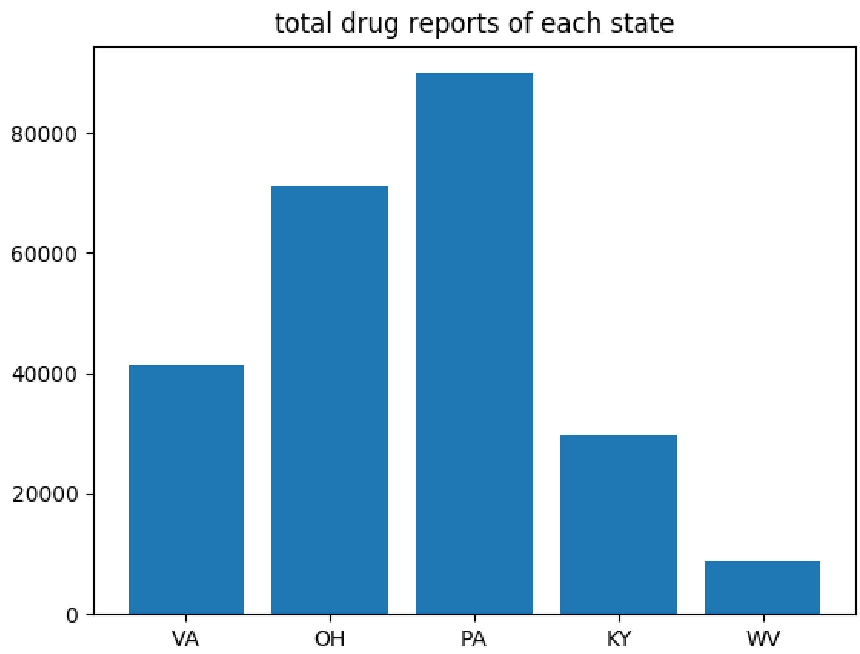


Figure 2: total drug reports of each state

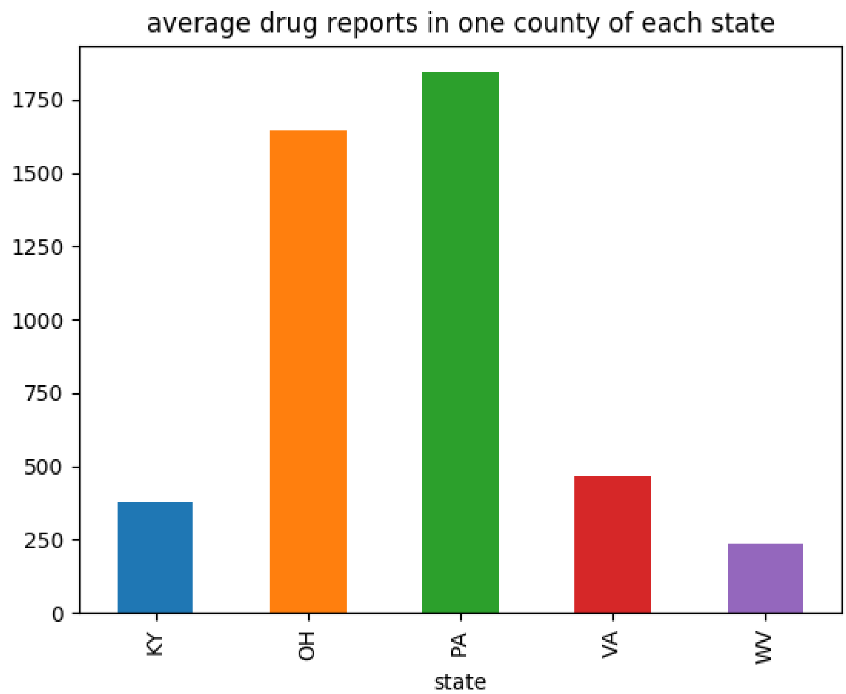


Figure 3: average drug reports of each state

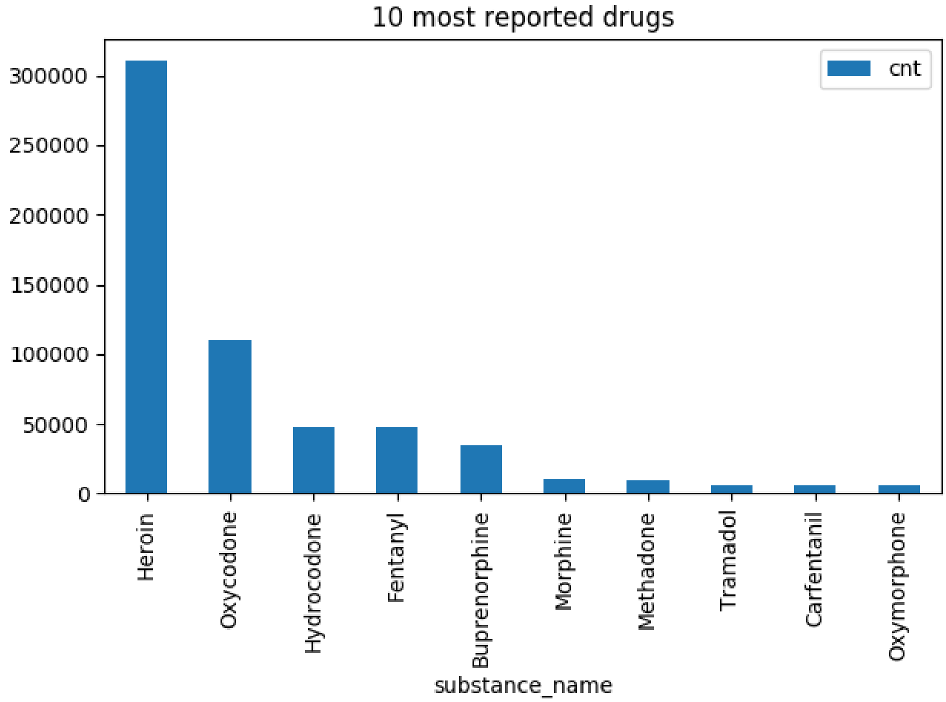


Figure 4: 10 most reported drugs

3.2 Linear Regression Model

3.2.1 Image Interpolation: Spline Interpolation

We use Spline Interpolation to fill in the drug-reported map. It is shown in appendix.

3.2.2 Linear Regression

We use the linear regression to predict the spread of drugs in terms of whether the pixel will be brighter or not. For each pixel of the drug-reported map, we fit the brightness comparing year in linear regression and the slope indicates the increase of the drug reports.

$$bright = k * year + b \tag{1}$$

where k and b are calculated in linear regression.

We create a change-map which is the heat map indicating the change of drug reports. If the slope i.e. k of one pixel in the linear regression is positive and is larger, the color of the pixel will be red and brighter, and vice versa.

As is shown in Fig.5, we can draw conclusion of the spread of drugs from this change-map. If the county or the region is significantly red which indicates the potential increase in drug reports, we think drugs tend to spread into this region. If the region is cool color, we think that the circumstance there will get better.

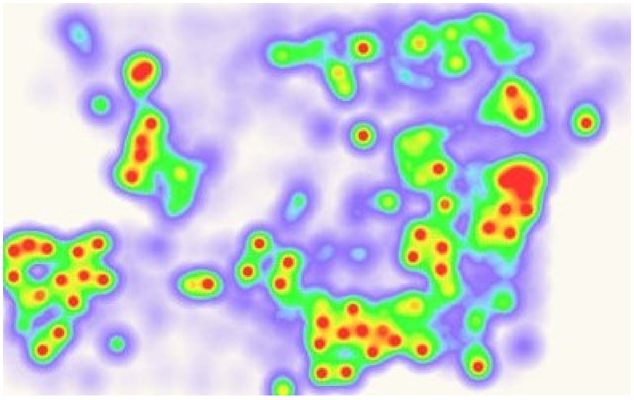


Figure 5: tendency of change of drug reports

3.3 Consideration about Socio-economic Data

In consideration of socio-economic data, we find that the economy and the community will significantly affect the tendency of drug spread. Thus, we use multiple variables to do linear regression, which improves our methods.

3.4 combination of NFLIS Data and Socio-economic Data

The spread of drugs is highly relevant to the condition of society and economy. They affect each other and is linearly relevant to some extent.

We propose that:

- The government should promote the economic development of poor regions especially regions with high drug reports.
- Education needs to be paid more attention which will promote economic growth and improve the quality of population in a long run.
- Government needs to attach significant to the centre of drug-reports and control the source of spread of drugs.
- Regions where drug reports tend to increase should prepare for it carefully.

4 Strengths and Weaknesses

4.1 Strengths

We establish ralationship between drug reports with several factors, which is relatively comprehensive and efficient. The mean square deviation is small which indicates the accuarcy of our model.

4.2 Weaknesses

- The relationship is relatively vague and complicated. We might need a model more than the linear relationship.
- We need to consider more factors to get a comprehensive view of the reasons of opioid crisis

References

[1] Elisa T. Lee, Oscar T. Survival Analysis in Public Health Research. *Go. College of Public Health*, 1997(18):105-134.

[2] Wikipedia: Proportional hazards model. 2017.11.26. `https://en.wikipedia.org/wiki/Proportional_hazards_model`

Apendix: The source codes

This Python program is used to fill in the image using interpolation. We use conjugate gradient descent to accelerate it.

Program 1: `interpolation.py`

```
import scipy.io as sio
import pandas as pd
import numpy as np
from PIL import Image
#get boundary matrix
boundary_data=sio.loadmat('boundary_intensity.mat')
boundary_data=boundary_data['image']
#300*300 image
n=300
#point inside image: 298*298
m=298
#only consider inner point
inner_pixel_cnt=m*m

# x_0=np.zeros(inner_pixel_cnt)
x_0=sio.loadmat("x_0.mat")
x_0=x_0['image'][0]
print(x_0.shape)

def matmul_A(x):
    res_list=[]
    for point_id in range(inner_pixel_cnt):
        tmp_val=0
        point_row=point_id//m
        point_col=point_id-point_row*m
        if point_row==0:
            if point_col==0:
                tmp_val+=4*x[point_id]
                tmp_val-=x[point_id+1]
                tmp_val-=x[point_id+m]

                # A[point_id][point_id+1]=-1

                # A[point_id][point_id+m]=-1
            elif point_col==m-1:
                tmp_val+=4*x[point_id]
                tmp_val-=x[point_id-1]
                tmp_val-=x[point_id+m]
                # A[point_id][point_id]=4
                # A[point_id][point_id-1]=-1

                # A[point_id][point_id+m]=-1
            else:
                tmp_val+=4*x[point_id]
                tmp_val-=x[point_id-1]
                tmp_val-=x[point_id+1]
                tmp_val-=x[point_id+m]

                # A[point_id][point_id]=4
                # A[point_id][point_id-1]=-1
                # A[point_id][point_id+1]=-1
```

```
            # A[point_id][point_id+m]=-1
    elif point_row==m-1:
        if point_col==0:
            tmp_val+=4*x[point_id]
            tmp_val-=x[point_id+1]
            tmp_val-=x[point_id-m]

            # A[point_id][point_id]=4

            # A[point_id][point_id+1]=-1
            # A[point_id][point_id-m]=-1

        elif point_col==m-1:
            tmp_val+=4*x[point_id]
            tmp_val-=x[point_id-1]
            tmp_val-=x[point_id-m]

            # A[point_id][point_id]=4
            # A[point_id][point_id-1]=-1

            # A[point_id][point_id-m]=-1

        else:
            tmp_val+=4*x[point_id]
            tmp_val-=x[point_id-1]
            tmp_val-=x[point_id+1]
            tmp_val-=x[point_id-m]

            # A[point_id][point_id]=4
            # A[point_id][point_id-1]=-1
            # A[point_id][point_id+1]=-1
            # A[point_id][point_id-m]=-1

    elif point_col==0:
        tmp_val+=4*x[point_id]
        tmp_val-=x[point_id+1]
        tmp_val-=x[point_id-m]
        tmp_val-=x[point_id+m]

        # A[point_id][point_id]=4

        # A[point_id][point_id+1]=-1
        # A[point_id][point_id-m]=-1
        # A[point_id][point_id+m]=-1
    elif point_col==m-1:
        tmp_val+=4*x[point_id]
        tmp_val-=x[point_id-1]
        tmp_val-=x[point_id-m]
        tmp_val-=x[point_id+m]

        # A[point_id][point_id]=4
        # A[point_id][point_id-1]=-1

        # A[point_id][point_id-m]=-1
        # A[point_id][point_id+m]=-1
    else:
        #not on the edge
        tmp_val+=4*x[point_id]
        tmp_val-=x[point_id-1]
        tmp_val-=x[point_id+1]
```

```
            tmp_val-=x[point_id-m]
            tmp_val-=x[point_id+m]

            # A[point_id][point_id]=4
            # A[point_id][point_id-1]=-1
            # A[point_id][point_id+1]=-1
            # A[point_id][point_id-m]=-1
            # A[point_id][point_id+m]=-1

        res_list.append(tmp_val)
    res_list=np.array(res_list)
    return res_list
    #construct A,b end


def conjug(n,b,x_0,N,TOL):
    x=x_0
    #step 1
    r=b-matmul_A(x)
    w=r
    v=w
    alpha=np.linalg.norm(w)
    alpha=alpha*alpha
    #step 2
    k=1
    #step 3
    while k<=N:
        print("loop "+str(k))
        #step 4
        norm_v=np.linalg.norm(v)
        # print("norm_v:"+str(norm_v))
        # if norm_v<TOL:
        #     return x
        #step 5
        u=matmul_A(v)
        t=alpha/np.inner(v,u)
        print(t)
        print
        if t<TOL:
            return x
        x=x+t*v
        r=r-t*u
        w=r
        beta=np.linalg.norm(w)
        beta=beta*beta
        #step 6
        if beta<TOL:
            if np.linalg.norm(r)<TOL:
                return x
        #step 7
        s=beta/alpha
        v=w+s*v
        alpha=beta
        k=k+1
    #step 8
    if k>n:
        print("the maximum number of iteration was exceeded")
```

```
b=np.zeros(inner_pixel_cnt)
# for i in range(inner_pixel_cnt):
#     b.append(0)


#construct b
for point_id in range(inner_pixel_cnt):
    point_row=point_id//m
    point_col=point_id-point_row*m
    if point_row==0:
        if point_col==0:
            # A[point_id][point_id]=4
            b[point_id]+=boundary_data[1][0]
            # A[point_id][point_id+1]=-1
            b[point_id]+=boundary_data[0][1]
            # A[point_id][point_id+m]=-1
        elif point_col==m-1:
            # A[point_id][point_id]=4
            # A[point_id][point_id-1]=-1
            b[point_id]+=boundary_data[1][299]
            b[point_id]+=boundary_data[0][298]
            # A[point_id][point_id+m]=-1
        else:
            # A[point_id][point_id]=4
            # A[point_id][point_id-1]=-1
            # A[point_id][point_id+1]=-1
            b[point_id]+=boundary_data[0][point_col+1]
            # A[point_id][point_id+m]=-1
    elif point_row==m-1:
        if point_col==0:
            # A[point_id][point_id]=4
            b[point_id]+=boundary_data[n-2][0]
            # A[point_id][point_id+1]=-1
            # A[point_id][point_id-m]=-1
            b[point_id]+=boundary_data[n-1][1]
        elif point_col==m-1:
            # A[point_id][point_id]=4
            # A[point_id][point_id-1]=-1
            b[point_id]+=boundary_data[n-2][n-1]
            # A[point_id][point_id-m]=-1
            b[point_id]+=boundary_data[n-1][n-2]
        else:
            # A[point_id][point_id]=4
            # A[point_id][point_id-1]=-1
            # A[point_id][point_id+1]=-1
            # A[point_id][point_id-m]=-1
            b[point_id]+=boundary_data[n-1][point_col+1]
    elif point_col==0:
        # A[point_id][point_id]=4
        b[point_id]+=boundary_data[point_row+1][0]
        # A[point_id][point_id+1]=-1
        # A[point_id][point_id-m]=-1
        # A[point_id][point_id+m]=-1
    elif point_col==m-1:
        # A[point_id][point_id]=4
        # A[point_id][point_id-1]=-1
        b[point_id]+=boundary_data[point_row+1][n-1]
        # A[point_id][point_id-m]=-1
        # A[point_id][point_id+m]=-1
```

```
    else:
        pass
        #not on the edge
        # A[point_id][point_id]=4
        # A[point_id][point_id-1]=-1
        # A[point_id][point_id+1]=-1
        # A[point_id][point_id-m]=-1
        # A[point_id][point_id+m]=-1
#construct A,b end



N=1000000
TOL=0.5
res_mat="inner_array_conjugate.mat"

img_array_inner=conjug(inner_pixel_cnt,b,x_0,N,TOL)
img_array_inner=img_array_inner.reshape((m,m))
sio.savemat(res_mat,{'image':img_array_inner})

print(img_array_inner)
```

This R program is used in linear Regression.

Program 2: `regression.r`

```
get_data<-function()
{
    xy_data=read.csv("xy_data.csv")
    return(xy_data)
}
xy_data=get_data()
linear_regression<- function()
{
y_x <- lm(y~x,xy_data)
print(summary(y_x))
return(y_x)
}
yx_regr=linear_regression()

scatter_plot<-function(plot_file)
{
    png(file=plot_file)
    plot(xy_data$x,xy_data$y,xlab='x',ylab='y',main='scatter␣point␣of␣linear␣regression'
    abline(yx_regr)
    abline(-1,0.5,lty=2,col='red')
    legend('topright',legend=c('sample␣regression','population␣regression'),lty=c(1,2),c
    dev.off()
}
scatter_plot('scatter_plot.png')
```